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ANNALS OF INTERNAL MEDICINE

VOLUME 29 NOVEMBER, 1948 NUMBER 5

BACTERIAL RESISTANCE TO ANTIBIOTICS *

By C. PHILLIP MILLER, M.D., F.A.C.P., *Chicago, Illinois*

THE development of resistance to the antibiotic drugs is a problem of theoretical interest to the bacteriologist and of practical importance to the clinician.

I should like to describe briefly some experimental studies on the development of bacterial resistance to penicillin and streptomycin and then discuss the clinical implications suggested by these laboratory observations.

DEVELOPMENT OF PENICILLIN RESISTANCE

Resistance to penicillin can develop in some bacteria, but it usually develops slowly. Meningococcus, for example, has been found to acquire resistance to penicillin if it is repeatedly subcultured onto media containing increasing concentrations of the drug. The graph in figure 1 plots the highest concentration of penicillin on which a strain of meningococcus was able to grow at each subcultivation.[1] Its resistance finally reached a level of 5,000 units per c.c. of media, a 16,600-fold increase, but this increase required 147 transfers.

Development of penicillin resistance has been explained by Demerec [2] as being due to the appearance of penicillin-resistant variants which arise in the bacterial population by the process of mutation. Fortunately, the degree of resistance possessed by any single mutant is but slightly greater than that of the original bacterial population in which it appears.[3] For that reason penicillin-resistance seldom proceeds rapidly.

Increase in resistance can also be produced in vivo. Figure 2 shows the development of resistance which occurred during the course of repeated passage through mice treated with subcurative doses of penicillin.[4] Each point on the graph represents the dose of penicillin which protected approximately 50 per cent of the mice (PD50) at each passage. This was determined at each inoculation by infecting several groups of mice and treating them with

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From the Department of Medicine, University of Chicago.

graded doses of penicillin. The PD50 rose slowly for a time, then rapidly to a level of 1,000 units. Above that level, additional resistance was acquired very slowly. We have no explanation to offer for the shape of this curve.

These experiments demonstrate that a penicillin-sensitive microörganism like meningococcus can acquire resistance both in vitro and in vivo but

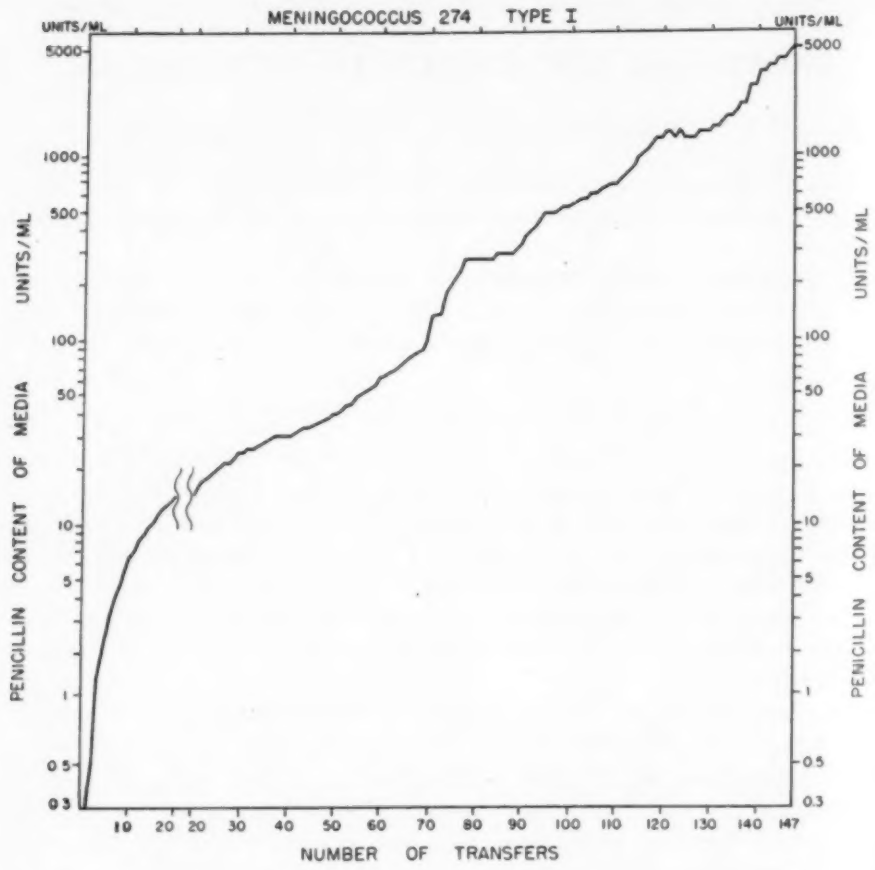

FIG. 1. Development of penicillin resistance by meningococcus during 147 transfers onto media containing increasing concentrations of the drug. The break after the twentieth transfer was occasioned by contamination of the strain which necessitated resumption of the series with a subculture which had been put away in the dry ice refrigerator.

usually at a slow rate even under the most favorable experimental conditions. This is the first of three reasons why resistance to penicillin so seldom becomes a serious practical problem for the physician in his clinical use of the drug. The second is the extraordinary effectiveness of penicillin in combating infection. Most sensitive bacteria are completely eliminated before they have time to develop resistance. The third reason is the cus-

tomary practice of administering penicillin in doses larger than is actually necessary for the control of most infections. Now that penicillin is relatively cheap and the supply abundant, doses are usually prescribed which provide a margin of safety sufficient to take care of some increase in resistance if it should occur. It is doubtful if any infections such as meningococcal meningitis, gonococcal urethritis, or pneumococcal pneumonia have been refractory to treatment because the organism has become resistant to penicillin.

Some strains of bacteria seem never to develop resistance even under

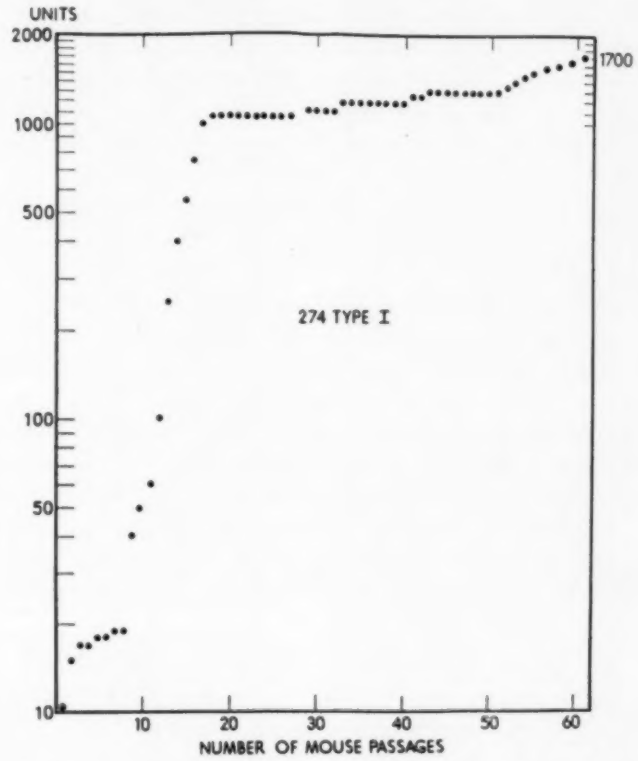

FIG. 2. Development of penicillin resistance by meningococcus in vivo. Dose of penicillin which protected approximately one-half of the mice at each inoculation.

carefully controlled experimental conditions. Gezon [5] has found, for example, that some hemolytic streptococci maintain their original sensitivity to penicillin in spite of prolonged cultivation on penicillin media. Others acquired resistance to such a slight degree as to be negligible from the clinical point of view.

On the other hand, some bacteria readily develop resistance to penicillin in vitro; e.g., staphylococci.[6]

Displacement of Penicillin-Sensitive by Penicillin-Resistant Bacteria

The foregoing remarks concern the development of resistance by bacteria originally sensitive to penicillin. This phenomenon must not be confused in clinical observation with the displacement of penicillin-sensitive by penicillin-resistant microörganisms during the course of treatment. Among the staphylococci, for example, some strains are naturally resistant. Most of the highly resistant staphylococci owe this property to their ability to elaborate penicillinase, a substance which inactivates penicillin.[7] These penicillinase-producing staphylococci are rather common and appear not infrequently as secondary invaders in infectious processes, such as wounds, which are exposed to contamination. Indeed, Barber [8] believes that such resistant strains are becoming more prevalent. In making cultures from infected areas care should be exercised to detect the presence of any penicillin-resistant staphylococci which may be present in small numbers. This can be done as Barber recommends by inoculating primary cultures onto media containing a strip of penicillin agar, the original ditch plate or trough plate method described by Fleming.[9]

When one of these highly resistant staphylococci is found after treatment in an open lesion such as a wound from which a sensitive staphylococcus was originally isolated, one is tempted to conclude that the original strain has developed resistance as a result of penicillin therapy. Such a conclusion is not warranted unless one can be quite certain that the possibility of secondary invasion has been ruled out or that the original cultures were not contaminated by small numbers of resistant bacteria which might have been overlooked. One must, therefore, be cautious about ascribing failure of cure to the development of resistance to penicillin unless one can be sure that an infection is being maintained by the same strain which initiated it.

Development of Streptomycin Resistance

In sharp contrast with the slow rate at which bacteria develop resistance to penicillin is their behavior toward streptomycin to which they can acquire a very high degree of resistance in a very short time.[10] Two or three transfers onto streptomycin media suffice to permit sensitive bacteria to grow abundantly on concentrations as high as 50,000 micrograms per c.c. This extraordinary increase in streptomycin resistance is due to the appearance of streptomycin-resistant variants which arise by mutation in a normal bacterial population.[11, 12] These mutants, unlike the penicillin-resistant mutants, are able to grow on high concentrations of streptomycin. They are also remarkable in that they consist of two types, both of which are resistant to streptomycin, but one of which can multiply only on streptomycin-containing media; that is, it is dependent on streptomycin for its growth.*

* This investigation was supported jointly by the U. S. Navy, Office of Naval Research, and the University of Chicago.

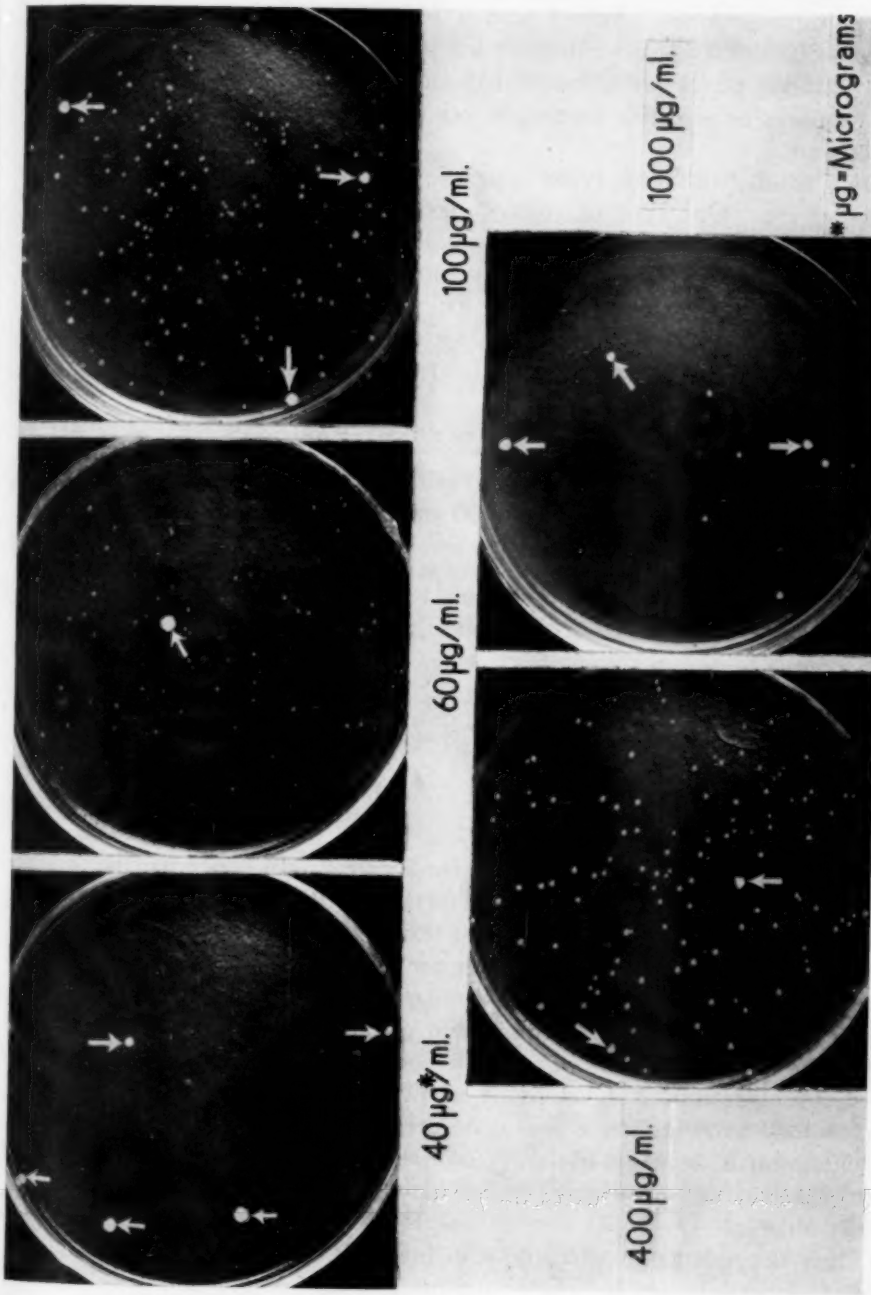

FIG. 3. Growth of meningococcus from equivalent inocula on graded concentrations of streptomycin 72 hrs. incubation.

Both types are easily demonstrable when heavy seedings of an organism like meningococcus are planted onto a series of plates containing graded concentrations of streptomycin as shown in figure 3. It should be borne in mind that the plates were inoculated simultaneously with approximately equal numbers of sensitive meningococci which had never been exposed to streptomycin.

Colonies of 2 different types appear on concentrations above 40 micrograms per c.c. One type of colony, designated type A, appears in small numbers on all concentrations. These colonies of meningococcus are highly resistant to streptomycin because they can be subcultured onto any concentration up to 50,000 micrograms per c.c. They will also grow on streptomycin-free media. They are virulent for mice, producing infections against which large doses of streptomycin afford no protection.

Streptomycin-Dependent Variants

The other type of colony, designated type B, always appears in greatest numbers on concentrations between 100 and 400 micrograms per c.c. These are streptomycin-dependent variants for they cannot be subcultured onto

Table I

Growth of Type B (Streptomycin-Dependent) Variants of Meningococcus in Broth

Concentration of Streptomycin	Growth
0 (Control)	0
10 micrograms/c.c.	±
40 micrograms/c.c.	+++
100 micrograms/c.c.	++++
400 micrograms/c.c.	++++
1000 micrograms/c.c.	+++
4000 micrograms/c.c.	±

media containing less than 5 micrograms per c.c. In other words, streptomycin has become a necessary growth factor for these organisms. Although the type B colonies appear in greatest numbers in this optimum concentration, they grow larger in size on higher concentrations. The increase in size seems to be due to a direct, stimulating action of streptomycin and is independent of the rate of establishment of colonies. When a large colony growing on media containing a high concentration is subcultured onto a lower concentration, it develops as small colonies, and conversely when a small colony growing on a low concentration is transplanted onto a high concentration it develops as large colonies. This fact indicates that all of these type B colonies are composed of identical organisms; i.e. they are genetically alike.

Their dependence on streptomycin in broth culture is shown in table 1. Growth occurred only in tubes containing streptomycin and was maximal in concentrations of 100 and 400 micrograms per c.c.

Dependent organisms do not differ (in morphology, sugar fermentations and type specificity) from normal meningococci except that they require streptomycin for their multiplication.

No substance has been found which will substitute for streptomycin in supporting growth of the dependent organisms, although we have tried a number of streptomycin derivatives; e.g., streptamine, streptidine, streptobiosamine and streptomycin which has been inactivated by cystein HCl and hydroxylamine HCl.

Experimental Infection with Streptomycin-Dependent Bacteria

The dependence of these organisms on streptomycin is demonstrable in vivo as well as in vitro. When inoculated into mice, they are unable to produce infection unless the animals are treated with streptomycin. Table 2 presents the results of a typical experiment. Three groups of mice were infected with different inocula of streptomycin-dependent meningococci. The second and third groups were treated with the drug and the first group served as untreated controls. The control mice, although inoculated with much larger numbers of meningococci, all survived, but those mice which were treated with streptomycin all died.

Table II

Results of Streptomycin Treatment of Mice Infected with Type B (Streptomycin Dependent) Variants of Meningococcus

Number of Meningococci Inoculated	Streptomycin Treatment	No. Mice	Result	Heart's Blood Cultures	
10,000,000	No treatment	6	All survived		
100,000	10,000 μgm. (in 4 doses) during first 12 hrs. of infection	12	All died	*Positive* on streptomycin media	*Negative* on streptomycin-free media
10,000		8	All died		

The heart's blood of each was cultured in duplicate onto streptomycin-containing and streptomycin-free media. All of the heart's blood cultures were positive on streptomycin media and negative on streptomycin-free media.

This experiment brings out 2 points: first, that these variants require streptomycin for multiplication in vivo as well as in vitro, and second that they retain their dependence on streptomycin after they have passed through the body of an infected animal host.

This is not a chance observation for it has been repeated many times. Nor is the demonstration of streptomycin-dependent variants an isolated finding. They, as well as type A variants have been recovered from all of 18 strains of meningococcus including types I, II and II alpha and from a number of other bacterial species, including *Escherichia coli,* several strains of Salmonella, *Aerobacter aerogenes, Proteus vulgaris, Pseudomonas pyocyanea, Staphylococcus albus* and *aureus* and alpha hemolytic streptococcus. These findings have been confirmed by Paine and Finland,[13] by Kushnick and his co-workers,[14] by Yegian and Budd [15] and by Rake.[16]

The fact that both types of variants have been recovered from a number of bacterial species indicates that this is a general phenomenon and is not restricted to any one group of microörganisms.

Certain metabolic peculiarities of these streptomycin-dependent variants are now being examined in the hope of obtaining an insight into the mechanism of action of streptomycin.

The Occurrence of Streptomycin-Resistant and Streptomycin-Dependent Bacteria in Animals and Man

The question naturally arises whether these streptomycin-dependent variants occur in nature or whether they develop only in vitro under the artificial conditions of laboratory experimentation.

This possibility has been investigated by treating normal rabbits and mice with large doses of streptomycin and making periodic cultures of the pharynx and large bowel. The cultures were made on media containing 400 micrograms of streptomycin per c.c. After a week both type A and type B variants were recovered from these animals.

We also made throat cultures on patients * who were being treated with streptomycin. It was found that streptomycin-resistant bacteria, including a small proportion of streptomycin-dependent bacteria, could be recovered from throats of those who had received 1 gram or more of streptomycin a day for more than two weeks.[17] Control cultures were made of the throats of patients who were not receiving streptomycin and of members of the hospital staff, students, and laboratory personnel and ward personnel. The cultures were all made by the author. The posterior pharyngeal wall was swabbed in the ordinary way and inoculated onto two agar plates containing 200 and 400 micrograms of streptomycin per c.c. Only streptomycin-resistant and streptomycin-dependent organisms were able to grow on these concentrations of streptomycin. With few exceptions, the bacteria which were isolated belonged to the ordinary species found in the flora of normal throats and were in no way related to the infections for which streptomycin was being administered.

Table 3 shows the results of these throat cultures. Ninety-eight per cent of the streptomycin-treated patients had positive cultures. These cultures were all positive by the thirteenth day of treatment. The 10 per cent of positive cultures from patients who were not receiving streptomycin contained relatively few organisms. Among 157 members of the staff, medical students and laboratory personnel, 4 per cent had a few resistant microörganisms on their plates. The highest incidence of positive cultures in our control group, 21 per cent, occurred among the nurses and maids working on the wards. All the strongly positive cultures came from nurses who were caring for patients receiving streptomycin. This series is too small to be significant, but it does suggest that streptomycin-resistant organisms which

* In the Albert Merritt Billings Hospital, University of Chicago Clinics.

develop in the throats of treated patients may be transferred to the nurses who look after them.

The organisms recovered on these cultures were all streptomycin-resistant. They were predominantly type A (resistant) organisms but a certain proportion were streptomycin-dependent (type B). These results together with those in the animal experiments mentioned earlier seem to settle the question whether streptomycin-dependent bacteria occur outside of the laboratory.

The microörganisms isolated from these cultures were the ordinary bacteria found in the normal human pharynx—staphylococci, streptococci, diphtheroids, Neisseriae, *M. tetragenus*—except that they included a higher proportion of yeast-like forms than is usually encountered. There was no evidence that any of these microörganisms was pathogenic.

Cultures on a second series of patients treated with small doses of streptomycin in a tuberculosis sanatorium * suggest that streptomycin-resistant bacteria appear more slowly in the throats of patients receiving only 0.5 gram a day.

TABLE III

Results of Throat Cultures on Media Containing Streptomycin

Source of Culture	Number of Individuals	Result			Per Cent Positive
		Negative	Positive		
			Few Colonies <25	Heavy Growth >25 Colonies	
Streptomycin-treated patients	59	1	5	53	98%
Untreated patients	70	63	4	3	10%
Ward personnel	99	78	7	14	21%
Staff, students and laboratory personnel	157	150	6	1	4%

SUMMARY

Resistance to penicillin can be developed by bacteria in vitro and in vivo but it proceeds relatively slowly. Resistance to streptomycin, on the other hand, can develop rapidly owing to the appearance of streptomycin-resistant variants which arise in a bacterial population by the process of mutation. These mutants are of two types, both of which are resistant and one of which is dependent on streptomycin for its growth in vitro and in vivo. Both types can arise among the normal microbial inhabitants of the upper respiratory passage of animals and patients during treatment with streptomycin.

* The Chicago Municipal Tuberculosis Sanitarium, Dr. George C. Turner, Superintendent, to whom the author is indebted for the opportunity to make these cultures.

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HEREDITARY HEMORRHAGIC TELANGIECTASES ASSOCIATED WITH PULMONARY ARTERIO-VENOUS FISTULA IN TWO MEMBERS OF A FAMILY *

By JOHN H. MOYER, Captain, M.C., and ALFRED J. ACKERMAN, Lieutenant Colonel, M.C., *Fort Sam Houston, Texas*

ALTHOUGH it is generally known that hereditary hemorrhagic telangiectases frequently involve visceral organs, the "cavernous hemangioma" of the lung is so rarely thought of that it usually remains unrecognized, even in the presence of mucocutaneous telangiectases. The clinical symptoms and signs which form the classical manifestations of this disorder are not infrequently attributed to congenital heart disease. Pulmonary opacities demonstrated radiologically have been usually misinterpreted, though they may be sufficiently characteristic to permit a correct early diagnosis.

In this presentation it is our intention to discuss the clinicopathological and radiologic manifestations of pulmonary arteriovenous fistulae observed in two members of a family suffering from hereditary hemorrhagic telangiectases. In one of these cases a cure was obtained after pneumonectomy.

CASE REPORTS

The family, which we are about to discuss, consists of the mother, two daughters and four sons all of whom are living. The father died at age 59 apparently of a pulmonary embolus secondary to phlebothrombosis of the leg. He was well until 20 years of age, when he first noted numerous telangiectases of the face and lips. The facial lesions were photosensitive, resulting in recurrent rupture of the vessels and bleeding on a direct exposure to sunlight. The lesions increased in number and severity until death. He also suffered from numerous attacks of epistaxis, frequently resulting in considerable loss of blood. About two weeks prior to his last hospitalization he ruptured a vessel in one leg while lifting a heavy weight. This was followed by a phlebothrombosis and a pulmonary embolus. His parents were apparently free from the disease.

The mother, 48 years of age, and two daughters, 22 and 19 years old, had several small cutaneous hemangiomata of the face and chest. These siblings exhibited also early small telangiectases of the lips, and the older daughter suffered in the past from recurrent epistaxis.

One son, 25 years of age, had similar early cutaneous and mucocutaneous telangiectases, a red cell count of 6.01 million with 16.5 grams of hemoglobin, and a hematocrit of 53 per cent. The reason for the polycythemia was not apparent, but it may have been indicative of an already existing, not yet demonstrable, congenital arteriovenous fistula of the lung.

The second son, 31 years of age, complained of frequent epistaxis. He first noted telangiectases on the face and lips at the age of 24. Shortly thereafter similar lesions appeared on the mucous membranes of the mouth, tongue and lips. They

* Received for publication September 8, 1947.

From the Brooke General Hospital, Brooke Army Medical Center, Fort Sam Houston, Texas.

have been increasing in number and have bled frequently. The hemorrhages were more severe following prolonged exposure to direct sunlight.

Physical examination disclosed numerous spider telangiectases over both malar prominences, on both lips, on the tongue, nasal septum and vestibule of the nose. There were several small subcuticular hemorrhages on the exposed part of the upper lip, which had a raised, blue appearance. Several small hemangiomata were scattered

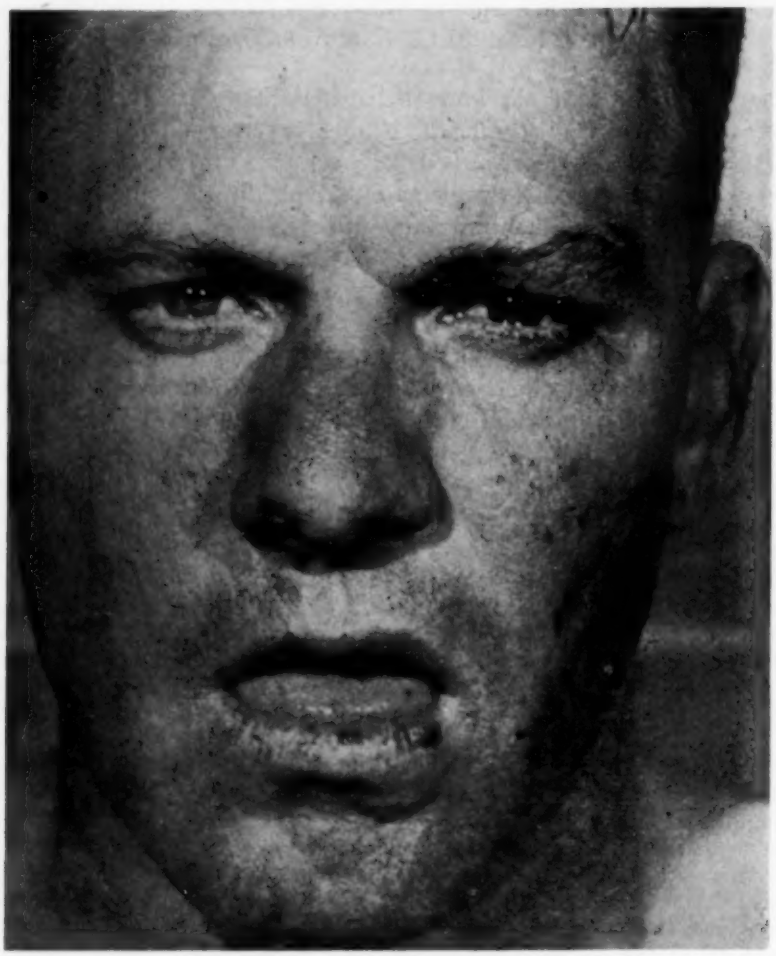

FIG. 1. *Case 1.* Multiple telangiectases of the face and the mucocutaneous junction of both lips.

over the upper chest and both arms. No other abnormalities were observed. Laboratory studies showed a normal blood count and hemoglobin.

The third son (case 1), a sergeant in the Regular Army, developed numerous telangiectatic spots and "blood blisters" involving the face and lips, about seven years ago. He has suffered from severe recurrent epistaxis which caused a significant loss of blood each time. Eight years ago, following heavy lifting, he had spontaneous hematuria with grossly bloody urine which lasted several days.

Physical examination revealed a well developed, well nourished robust male. There were numerous spider nevi over both malar prominences, and numerous small telangiectases on the lips, tongue and right vestibule of the nose, varying in size from pin-head to 0.25 centimeter. There were also numerous subcuticular hemorrhages on the lips. Three small hemangiomata were present on the chest. Examination of the chest and heart was negative, except for an accentuated aortic second sound, which was transmitted to the axilla. The tourniquet test was negative and funduscopic examination of the retina revealed no hemorrhages or vascular abnormalities.

FIG. 2. *Case 2.* Multiple telangiectases of the face and the mucocutaneous junction of the lower lip.

Radiologic examination of the chest revealed a round area of increased density in the left lung field at the level of the fourth rib anteriorly measuring 2 centimeters in diameter. There was a vessel leading from the left pulmonary artery to this area. These findings were thought to be consistent with a small arteriovenous fistula. Angiography revealed dye within the previously described round opacity. Two vascular bands connected this opacity with the hilar vessels. The superior band was rather tortuous and of slightly greater width. On intravenous urography the collecting systems of both kidneys were well visualized by the dye. The superior lateral margin of the right renal pelvis was slightly concave. The upper calyx was possibly compressed near its junction with the pelvis. There was no other evidence of abnor-

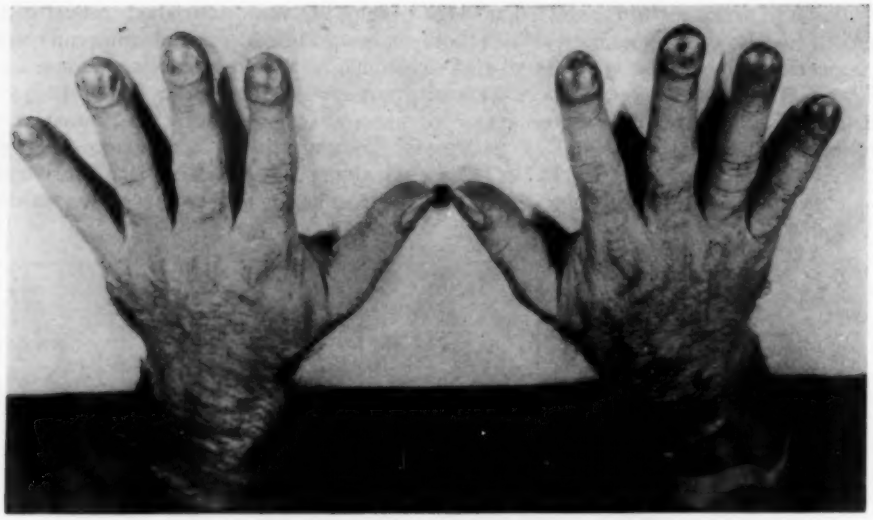

FIG. 3. *Case 2.* Marked clubbing of the phalanges and acrocyanosis.

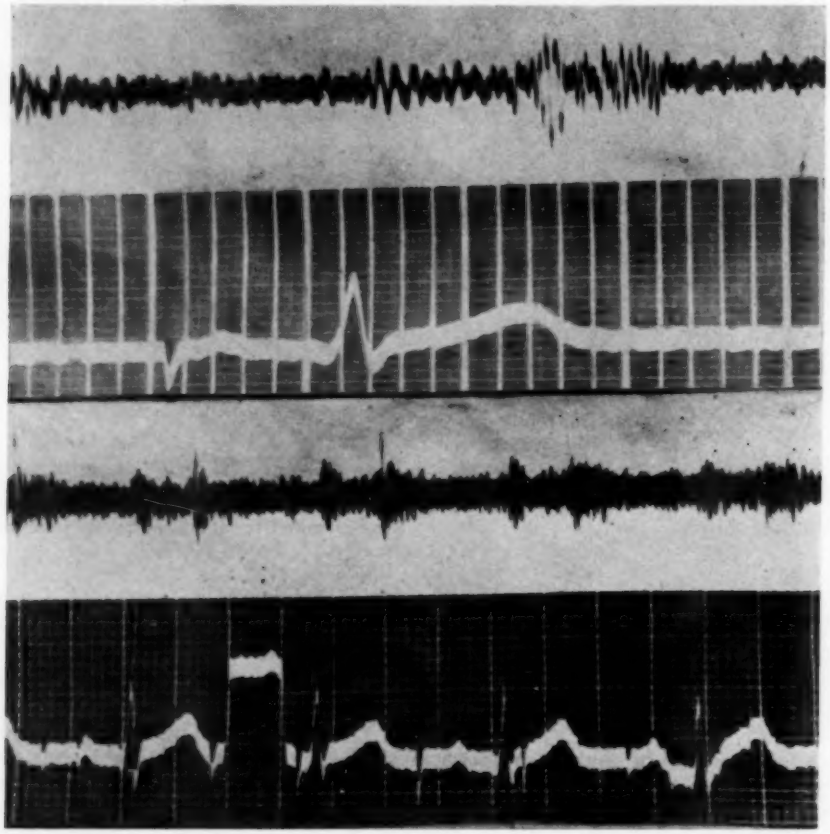

FIG. 4. *Case 2.* Stethogram demonstrating the murmur during the diastolic phase of the cardiac cycle.

mality. In view of the history of so-called "essential hematuria" these findings suggested the possibility of a hemangioma within the kidney. Laboratory studies revealed a red cell count of 4.8 million; a white cell count of 10,000; 15.5 grams of hemoglobin; a hematocrit of 44 per cent; a differential of 64 per cent polymorphonuclears, 32 per cent lymphocytes, 2 per cent eosinophiles, 2 per cent monocytes; a blood volume of 9,300 c.c. determined by the Congo red method; a plasma volume of 64 c.c./1 kg.; a cell volume of 50 c.c./1 kg.; and an icteric index of 4.

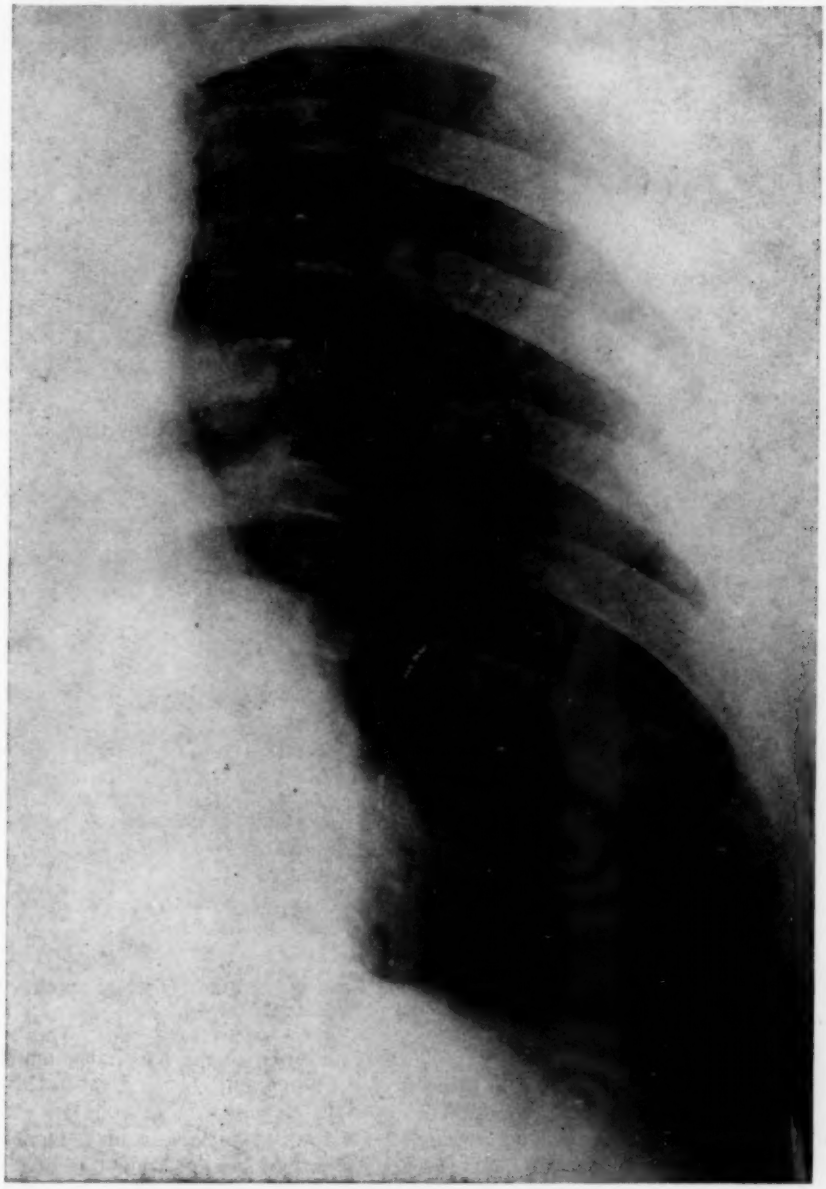

FIG. 5. *Case 1.* PA roentgenogram showing a small round opacity at the level of the fourth rib anteriorly.

FIG. 6. *Case 1.* Left lateral roentgenogram: the opacity lies anteriorly and appears to be connected with an abnormal pulmonary vessel.

The fourth son (case 2), 26 years old, was admitted to the hospital complaining of attacks of dizziness lasting two to three days. The patient was in good health until 1936, when he had pneumonia, followed by persistent cyanosis. In 1941 he was admitted to an army hospital, complaining of generalized malaise and a moderately severe upper respiratory infection. He had a cough which was productive of a small amount of mucopurulent sputum. The infection subsided within a few days. About a week after hospitalization he developed phlebothrombosis of the right saphenous vein,

which, however, subsided after six or seven days without therapy and without complication. This was followed by episodes of blurred vision, dizziness, weakness and vertigo, not associated with nausea, or vomiting, and lasting only five to ten minutes. The complaints were relieved when the patient was in a prone position and were more severe in an upright position. The episodes recurred approximately every two to three weeks during his original two months of hospitalization. Roentgenograms of the chest revealed a round mass measuring 5 cm. in diameter lying against the

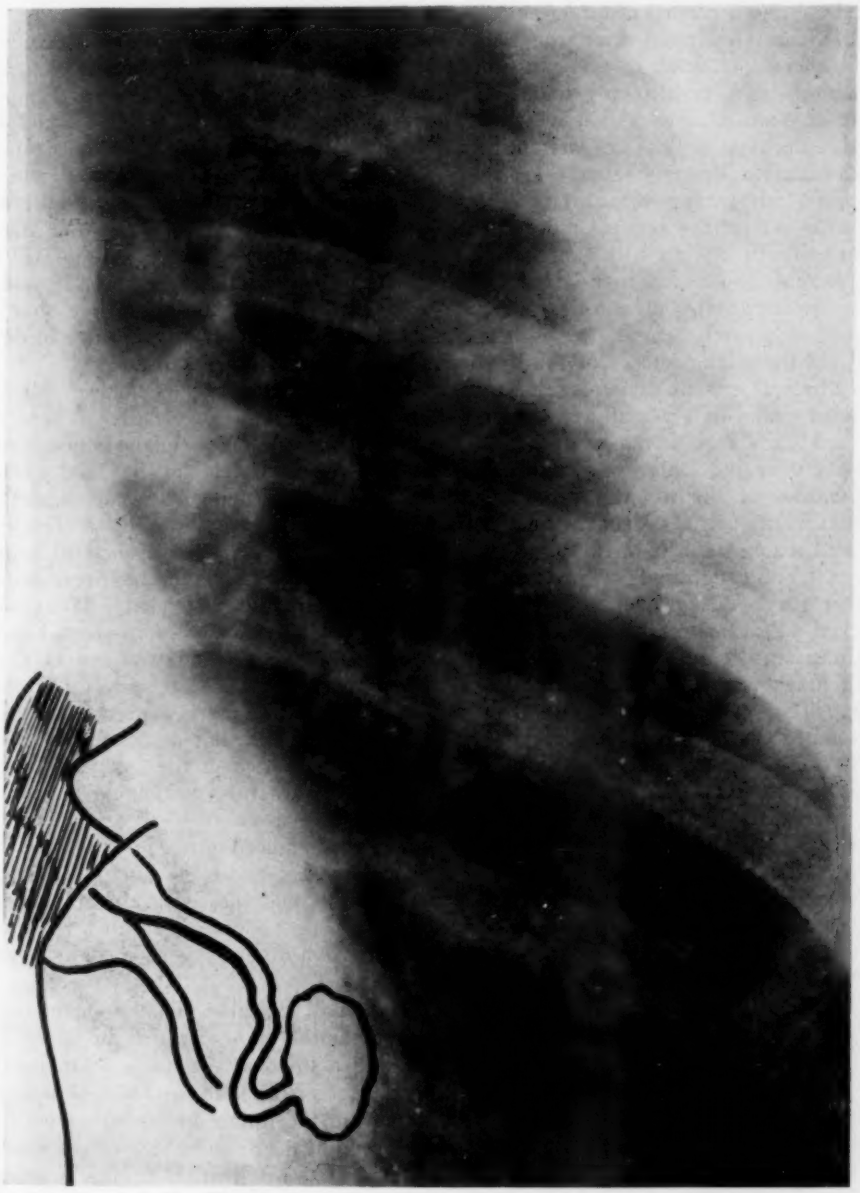

FIG. 7. *Case 1.* Angiogram: the arteriovenous fistula and its communicating vessels are visualized.

posterior chest wall. It was thought to be localized in the lower portion of the posterior mediastinum, and a presumptive diagnosis of neurofibroma was made. Laboratory studies revealed: red cell count of 8.9 million; hemoglobin 125 per cent; white cell count of 10,450 with 75 per cent neutrophiles; 23 per cent lymphocytes; and 2 per cent monocytes. A Schilling count showed 42 per cent segmented forms; 31 per cent band forms; 15 per cent large lymphocytes; 8 per cent small lymphocytes; and 2 per cent metamyelocytes. The urine was normal. Repeated blood studies showed a red cell count of 9.6 million; a white cell count of 3,500 with 638,800 platelets; and a normal differential count.

He was separated from the Service in April, 1941, with a diagnosis of (1) polycythemia, chronic, severe, cause undetermined, and (2) thrombosis, simple, great saphenous vein, right, cause undetermined. He continued to complain of dizziness, weakness, and blurred vision which became sufficiently severe to cause marked diplopia. Between attacks he was entirely asymptomatic except for exertional dyspnea. Immediately following separation from the Army, the above mentioned symptoms occurred only every two to three weeks and lasted for several minutes to several hours. Recently, they have become more severe, confining the patient to bed. The attacks seem to be precipitated by exertion or hot weather. About three years ago (1943) the patient first noted that he had developed clubbing of the fingers and multiple spider telangiectases on the lips, face, and over the bridge of the nose. He also had several moderately severe attacks of epistaxis and observed that on exposure to direct sunlight the telangiectases of the lips frequently ruptured and bled.

Physical examination revealed a well developed, well nourished male, with generalized cyanosis, especially marked on the lips, tongue and fingernails. There was marked clubbing of the fingers and toes. Numerous spider telangiectases were present over the malar prominences and on the upper and lower lips and mucous membranes of the tongue and buccal mucosa. Accompanying these telangiectases were several areas of subcuticular hemorrhage, especially on the lips. The eyes showed marked conjunctival injection with several areas of subconjunctival hemorrhage. The eyegrounds were normal. Pharyngeal mucous membranes were normal except for a dusky hue. The neck veins were markedly distended. There were marked pulsations of the carotid arteries, noted especially in the supra-sternal notch. No murmurs were heard over the neck vessels and the thyroid was not enlarged. Both lungs were apparently normal. The blood pressure was 130 systolic; 80 diastolic. The pulse rate was 80 and of regular rhythm. A marked precordial thrust was noted in the fifth interspace in the mid-clavicular line not associated with any thrill or systolic murmur. A diastolic murmur was audible over the second left costal interspace, transmitted to the third interspace. There was also a blowing murmur in the paravertebral region near the angle of the right scapula over an area about the size of the palm of the hand. This was very pronounced during inspiration and barely audible during expiration. The phase of the cardiac cycle during which the murmur was heard was confirmed by a stethogram which showed a murmur extending through the early and mid-diastolic phases. The abdomen revealed no abnormalities. The liver and spleen were not palpable. All other systems were apparently normal.

Radiologic examination of the chest revealed a circular shadow of increased density in the right lower lung field, which lay near the apex of the right lower lobe. The infero-lateral margin of this density showed a bi-convex contour. On fluoroscopy a slight pulsation of the pulmonary opacity could be seen, and the oblique and lateral views showed a large vessel extending from the hilum and merging with the described shadow. The Valsalva test showed a slight decrease in size of the opacity, and the Mueller test showed an increase in size. Visualization of the heart and great vessels by 50 c.c. of 70 per cent Diodrast demonstrated the dye within the mass.

TABLE I

Hematological Determinations

Preoperatively			Postoperatively		
Date	Examinations	Values	Date	Examinations	Values
Feb. 26, 1947	Red cell count	8.2 million	Mar. 9, 1947	Red cell count	6 million
	White cell count	5,500		Hemoglobin	17 gm. %
	Differential:		Mar. 11, 1947	Red cell count	5.0 million
	Neutrophiles	70%		Hemoglobin	15 gm. %
	Lymphocytes	26%		Hematocrit	53%
	Eosinophiles	4%	Apr. 4, 1947	Red cell count	5.1 million
Feb. 28, 1947	Red cell count	8.4 million		Hemoglobin	15 gm. %
	Hemoglobin	22.8 gm. %			
	Platelets	130,000			
	Hematocrit	60%			
	Reticulocytes	2.6%			
	Bleeding time	1.5 min.			
	Clotting time	2.5 min.			

TABLE II

Preoperative Biochemical Studies of the Blood

Date	Examination	Value	Date	Examination	Value	Remarks
Feb. 20, 1947	Serum protein	8 gm. %	Feb. 21, 1947	Cholesterol	130 mg. %	Electrolyte studies were not repeated because the values were within normal limits and were not expected to change.
	a. Globulin	2.8 gm. %		Sugar (blood)	97 mg. %	
	b. Albumin	5.2 gm. %		Non protein nitrogen	55 mg. %	
Mar. 2, 1947	*Prothrombin time	22 second		Serum sodium	374 mg. %	
	Blood urea nitrogen	24 mg. %		Serum potassium	17.1 mg. %	
Mar. 5, 1947	Icteric index	6		Serum calcium	9.7 mg. %	
	Uric acid	2.6 mg. %		Serum phosphorus	2.8 mg. %	
	Creatinin	2.2 mg. %		Plasma chlorides	486 mg. %	
				CO_2	60 vol. %	

* Control—17 seconds.

TABLE III

Blood Oxygen Saturation

Preoperatively		Postoperatively	
* Determination	Value	† Value	Remarks
Hemoglobin	22.8 gm. %	15.4 gm. %	The critical level for cyanosis is 5 grams of reduced hemoglobin.
Blood oxygen capacity	30.2 vol. %	19.3 vol. %	
Arterial blood content (femoral)	19.1 vol. %	17.4 vol. %	
Venous blood content (brachial)	11.1 vol. %	11 vol. %	
Oxygen saturation arterial blood	63%	90%	
Oxygen saturation venous blood	40%	57%	
Arterial blood unsaturation	11.1 vol. %	——	
Reduced hemoglobin in arterial blood	8.4 gm. %	1.9 gm. %	
Venous blood unsaturation	19.1 vol. %	——	
Reduced hemoglobin in venous blood	14.4 gm. %	8.3 cm. %	
Average reduced hemoglobin (arterial + venous blood)	11.4 gm. %	5.1 gm. %	

* Duplicate samples were examined and were found correct with 5% of error.
† Three days postoperatively.

TABLE IV

Studies of Blood Volume and Pertinent Blood Constituents

Preoperatively			Postoperatively		
Date	Examination	Value	Date	Value	Remarks
Mar. 3, 1947	* Blood specific gravity	1.068	Mar. 10, 1947	1.056	* By the copper sulfate method
	Plasma specific gravity	1.028		1.024	
	Plasma protein	7.82 gm. %		7.6 gm. %	** Congo red method
	Hemoglobin	21.5 gm. %		15 gm. %	
	Hematocrit	58%		42%	*** Normal: 37 c.c./kilo
Mar. 4, 1947	** Total blood volume	12,900 c.c.		7,625 c.c.	
	Blood volume/kilo	161 c.c.	Mar. 10, 1947	95 c.c.	**** Normal: 51 c.c./kilo
	*** Cell volume/kilo	99 c.c.		40 c.c.	
	**** Plasma volume/kilo	62 c.c.		55 c.c.	
	Per cent cell volume Increase above normal	160%		Normal	
	Per cent plasma volume Increase above normal	21%		Normal	

The radiologic findings were consistent with an arteriovenous fistula. Fluoroscopic and radiographic examination showed a normal configuration and size of the heart. All cardiac chambers were within normal limits. The long bones were normal.

Extensive laboratory studies were performed with special reference to physical characteristics of the circulating blood. Most of the pertinent studies were repeated after pneumonectomy. The essential laboratory data are reproduced in tables 1 through 4, and we shall refer to them whenever this is necessary. The vital capacity was 110 per cent; the venous pressure was 13 cm. of water; the circulation time from arm to tongue was 12 seconds and from arm to lung 9 seconds; the Wassermann reaction was negative.

The patient remained ambulatory while on the Medical Service, and suffered no syncopal episodes similar to those described previously.

On March 8, 1947 a total right pneumonectomy was performed by the Surgical Service. On the second postoperative day the patient was out of bed and was gradually made ambulatory. It spite of this, on the fifth day he developed phlebothrombosis of both lower extremities, necessitating ligation of the superficial femoral veins bilaterally. The subsequent clinical course was uneventful except for a low grade fever which subsided spontaneously.

DISCUSSION

Hereditary hemorrhagic telangiectases were recognized by Rendu [39] in 1896, when he reported a case of hereditary epistaxis associated with multiple hemangiomata of the skin and mucous membranes. They were not described, however, as a clinical entity until 1901, when Osler [33] reported three cases of hereditary epistaxis associated with angiomata of the nasal septum and multiple telangiectases of other mucous membranes and of the skin. Since that time there have have been well over 1,000 cases reported in the literature and the lesions have been found to involve practically any area of the body.[5]

The clinical manifestations of hemorrhagic hereditary telangiectases are quite varied depending upon the severity of the disease, the fragility of the

involved vessels and the site of involvement. Repeated hemorrhages result in secondary anemia, chronic debility and if severe, death.[49]

The hereditary nature of the disease has been fairly well established. A vascular defect is apparently transmitted as a dominant characteristic[34] affecting both sexes, but more frequently the female. In families with hereditary hemorrhagic telangiectases, approximately one-third of the mem-

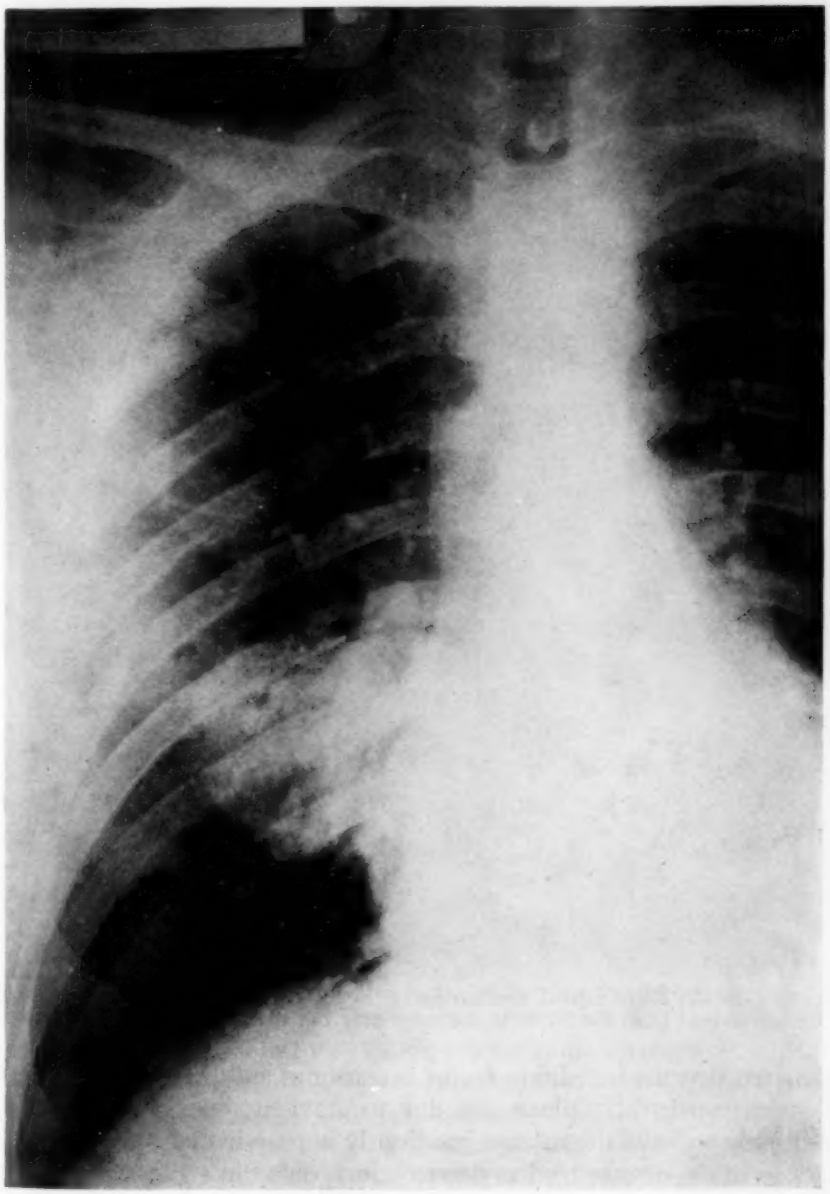

FIG. 8. *Case 2.* PA roentgenogram of the chest revealing the enlarged hilar vessels and the well-defined vascular "tumor."

bers are felt to be affected by this disorder.[51] The disease has been observed in three and four generations of families in whom they occur. Teahan [51] was able to trace it through six generations. According to some observers, the disease occurs spontaneously in 20 per cent of the cases.[49] Fitz-Hugh [12]

FIG. 9. *Case 2.* Right lateral roentgenogram of the chest: large abnormal pulmonary vessels extend from the hilum to the mass near the apex of the right lower lobe.

emphasized that the hereditary factor is constant, and that where it could not be demonstrated, this failure was due to atavism; one generation may be spared, only to have the disease insidiously appear in the next. The manifestations of the disease tend to decrease in severity in successive generations as well as to vary from one generation to another.

The most outstanding characteristic other than the hereditary tendency

is the formation of abnormal vessels, which bleed very easily even after slight trauma.

Singer and Wolfson [45] contended that the disease is usually a gross deviation of capillary formation, representing a generalized process rather than a local developmental defect of small vessels. There is frequently a marked photosensitivity as manifested in the family observed by us. Oc-

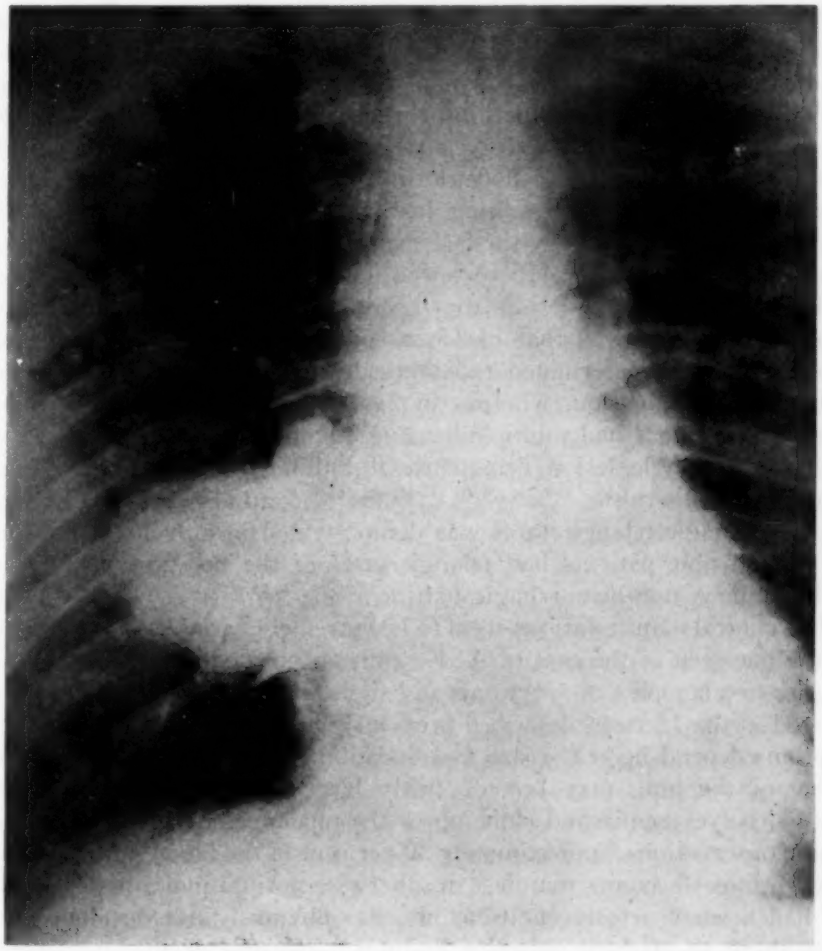

FIG. 10. *Case 2.* Angiogram: the dye is collected within the vascular mass; the vessels leading into the mass are also visualized and considerably dilated.

casionally telangiectases fail to exhibit hemorrhagic characteristics.[28] Perhaps Fingerland and Janoušek [12] gave some explanation for these variations, when they found that the disease tends to be more severe in people with dark complexion. The abnormal vessels usually appear between the ages of 20 and 30, and attain full development in the fourth decade although the age of onset has varied between three months and 67 years of age. In the

family observed by us the skin lesion first appeared between the ages of 22 and 25.

The first case of pulmonary hemangioma was found incidentally by De Lange, De Vries and Rables [11] on postmortem examination of a two and one-half year old child. Later Wollstein [57] reported a malignant hemangioma of the lung in a four month old child which died from the disease and Hall [17] described similar postmortem findings in a 40 year old woman.

Although Rhodes had been credited with the first clinical description of hemangioma of the lung, Reading [37] earlier described the clinical triad of clubbing, cyanosis and polycythemia, associated with a pulmonary lesion which on postmortem examination proved to be a hemangioma of the lung. The patient died of a brain abscess. There were no additional clinical reports on this subject until Rhodes [40] in 1938 reported a case of cavernous hemangioma of the lung resulting in a fatal hemorrhage. The rarity of the disease is also attested by the fact that Sisson and his co-workers [46] found no record of it among 19,415 reviewed postmortem examinations at Johns Hopkins Hospital. The lesions may be either single or multiple. A review of the literature showed that of 15 cases reported, 10 patients had single pulmonary lesions determined radiologically or confirmed by operation or postmortem examination, whereas in five cases the lesions were multiple. In our cases, case 2 had multiple hemangiomata proved at operation, while A. E. had a single lesion demonstrated radiologically. Of the 15 cases reported in the literature [1, 8, 15, 18, 20, 21, 25, 29, 42, 46, 47] an association with hereditary hemorrhagic telangiectases was demonstrated in only three instances,[1, 25, 42] though nine patients had telangiectases of the nose, face or lips of a non-hereditary, non-hemorrhagic nature.[1, 15, 20, 25, 29, 37, 42, 46]

The clinical manifestations seem to be extremely variable. Small fistulae, like the one seen in the case of A. E., cause no complaints while large ones give rise to a complex of symptoms and signs which almost characteristically occurred in the 15 cases described previously and in our patient C. E. The symptoms depend upon the size and duration of the shunt. Arteriovenous fistulae of the lung may become fairly large before the typical triad of cyanosis, polycythemia and clubbing of the phalanges develops. According to some observations, approximately 30 per cent of the blood must be shunted before cyanosis becomes manifest in otherwise normal individuals.[29] A. E., who had a small arteriovenous fistula, has obviously not developed a sufficient shunt to produce objective findings. Because of that, an operation at this time was not deemed advisable. Further observation of the patient was, however, recommended, because he has already had spontaneous epistaxis and spontaneous hematuria and he may well develop spontaneous hemorrhage from the lung.

The symptoms of this disease usually become manifest in the third decade of life. Our patients were 26 and 29 years of age respectively. Except for the clubbing of the fingers and toes the exact origin of which remains obscure the chief symptoms of the disease are apparently due to chronic anoxemia,

produced by incomplete aeration of the blood in the lungs. This stimulates the erythropoietic system resulting in polycythemia. Other symptoms such as dyspnea on exertion, weakness, palpitation, dizziness, numbness, faintness, diplopia, thick speech, hemoptysis, emesis and chest pain represent secondary phenomena.

Our patient (case 2) showed the typical triad of cyanosis, polycythemia and clubbing of the fingers and toes, and also other symptoms related to anoxemia.

Cyanosis has varied as to the time of appearance from shortly after birth to a period only several years prior to the time when the patients sought medical attention.[29] In our patient (case 2) the cyanosis became manifest at the age of 22. Clubbing of the fingers usually develops shortly after cyanosis becomes manifest.

The effects of anoxemia due to pulmonary shunt and the compensatory mechanisms are interesting from a clinical and a laboratory point of view. The compensatory changes consist of an increase of blood volume (affecting the cell volume rather than the plasma volume), increased hemoglobin concentration and an increase of erythrocytes closely paralleling the changes seen in the relative anoxia of subjects living at high altitudes for long periods of time. In both conditions these changes are proportional to the degree of unsaturation of arterial blood regardless of geographical location or race.[19] Barcroft [4] in 1923 pointed out that residents living at high altitudes had decreased blood oxygen tension with an increased cell volume and red blood cell concentration. McFarland et al.[31] who examined 200 civilian pilots found the red cell count above six million in 50 per cent of flying personnel. Smith et al.[47] found 19 per cent increase of cell volume in residents at high altitudes, but normal plasma volume. Certain observations tend to substantiate the contention that polycythemia of the newborn is also due to low intrauterine oxygen tension.[14] Hurtado et al.[19] found that the response to acute anoxia was short, the increase of the red cells was transitory, due largely to hemo-concentration, but as the subjects remained exposed to low oxygen tension, the increased erythropoietic activity became a constant factor, causing an increase of reticulocytes (2 to 4 per cent) and of the cell volume without a concomitant increase of plasma volume and without change of plasma proteins. This change lasted as long as the subjects remained in this environment and was proportional to the degree and duration of the anoxia. It is remarkable how well patients with pulmonary arteriovenous fistula conform to the same principles.[1, 15, 18] In several instances red cell counts up to 11.4 million and a corresponding rise of the hemoglobin content were observed.[15, 40, 46] In both conditions there is an inverse ratio between the polycythemia and the arterial oxygen saturation.[1, 15, 18, 19] In view of these findings, it is not surprising that the polycythemia reflects fairly accurately the degree of arteriovenous shunt in cases of pulmonary arteriovenous fistulae. Values of 70 per cent of oxygen saturation were recorded in three cases.[15, 40, 46] Case 2 had only 63 per cent oxygen saturation (see

table 3). His cell volume rose 160 per cent above the normal value, while the plasma volume increased only by 21 per cent (see table 4). It is probable that our and the other patients obtained maximal compensation (see table 3).[1, 15, 18] If the fistula continued to increase in size, one should expect eventually a decrease of the red cell count due to depression of the bone marrow secondary to anoxia.[19] The critical point of arterial oxygen saturation at which suppression of erythropoiesis might be expected is not known. Taussig and Blalock observed that children suffering from congenital heart disease developed polycythemia when the arterial oxygen saturation was only 36.3 per cent. Indeed it appeared that in their cases an arterial blood saturation of 66 per cent or lower was necessary, before a compensatory polycythemia became manifest. One of those cases, however, with only 20.6 per cent of saturation, did show evidence of bone marrow suppression and anemia. Normal blood counts or slight anemias also occurred in patients with pulmonary arteriovenous fistulae, when they were associated with another disease or frequent excessive hemorrhages.[25, 42]

Already in 1878 Bert [6] expressed the opinion that the erythroblastic activity of the bone marrow was governed by arterial oxygen tension. Probably due to physiological adjustment there is a less significant erythropoietic response in chronic anoxemia than in the subacute phase.[19] Immature red cells and marked increase of reticulocytes are therefore not usually seen in pulmonary arteriovenous fistulae. Our patient showed no nucleated red cells and a reticulocyte count of 2.6 per cent. In contradistinction to polycythemia vera there was no increased activity of the granulocytic series, and the spleen was not enlarged.

Chronic anoxemia of whatever origin does not modify permanently the activity of the erythropoietic system.[19] This was conclusively demonstrated in "altitude polycythemia" and was also confirmed in the patient (case 2), who three days after pneumonectomy showed a return to normal of the red cell count, total cell volume, and hemoglobin concentration (see tables 1, 2, and 4).

The lack of cardiac enlargement was significant and essentially in conformity with the findings of other writers on this subject. An enlarged heart was observed in only two cases, one of whom had mitral stenosis.[25] In the other case the enlargement was due to congestive failure secondary to chronic myocardial disease.[46] Kennedy and Burwell [22] have noted that in chronic peripheral arteriovenous fistulae there is an increase in cardiac output, blood volume, and venous oxygen tension near the fistula, and mild to moderate cardiac hypertrophy. The lack of cardiac hypertrophy in cases of chronic pulmonary arteriovenous fistulae has been attributed to the low pressure in the pulmonary circulation.[15]

The blood pressure is usually within normal limits.[42] A murmur is commonly heard over the tumor mass and is transmitted to the heart; it is continuous, with maximal intensity in late systole and early diastole. The murmur is loudest on deep inspiration and hardly audible on expiration.[21,

[25, 42] This, however, is not sufficiently pathognomonic, since murmurs have been described during other phases of the cardiac cycle and over the heart only. No murmur of any kind was recorded in five cases.[1, 18, 25, 42, 47] One of our patients (case 2) had a purely diastolic murmur, of increased intensity on deep inspiration. The murmur disappeared after pneumonectomy. The other patient (case 1) had no cardiac murmurs.

Pulsation of the carotids and in the suprasternal notch may be very prominent. In the majority of cases the electrocardiograms were normal. One case [21] showed marked right axis deviation. This possibility should be kept in mind in differentiation of this condition from congenital heart disease. In case 1 the electrocardiogram was normal. The other patient (case 2) had marked left axis deviation. Electrocardiograms taken during the operation showed, for the most part, nodal tachycardia with auricular and ventricular extrasystoles. During bronchoscopy the tracing showed a supraventricular tachycardia with a rate of 150 per minute. A tracing taken the day following operation showed a smaller S_2 and S_3. CF leads showed a "V" QRS in $CF_{1, 2, 3, 4 \text{ and } 5}$.* The electrocardiographic findings were difficult to interpret because the heart was not in transverse position nor was there any apparent left sided hypertrophy.

The prognosis in cases of pulmonary arteriovenous fistulae has been good especially in those operated upon. Two patients [8, 42] died following a rupture of the fistula into a bronchus with a hemorrhage; one patient [46] died shortly after cardio-angiography and six [1, 18, 20, 21, 25] who have been operated upon are living and well. Other patients remain under medical observation because the disease is relatively asymptomatic, or because an operation was refused. The possibility of a hemorrhage as well as vascular thrombosis due to increased viscosity of the blood, must always be kept in mind in these patients.

Pathology

Hereditary telangiectases are characterized by disseminated abnormalities of capillaries, small venules and small arterioles, which have the appearance of hemangiomata or telangiectases or both.[53] They vary from typical spider nevi to pea size hemangiomata.[34, 49] They occur most commonly on the skin and mucous membranes, but may involve any organ. The cutaneous or mucosal vascular lesions are composed of dilated small vessels which histologically comprise a single layer of endothelium underneath a much thinned layer of epithelium. The absence of muscular and elastic layers of the vessel wall is conspicuous. The vessels are fragile and rupture easily. Thrombosis is quite frequent [49] and possibly accounts for occasional disappearance of the lesions in certain areas. Neumark [32] has shown that in addition to the hyperplasia of the small vascular radicles there are changes in the connective tissue consisting of degeneration of conjunc-

* We wish to express our appreciation to Lt. Walter Zimdahl for the electrocardiographic studies.

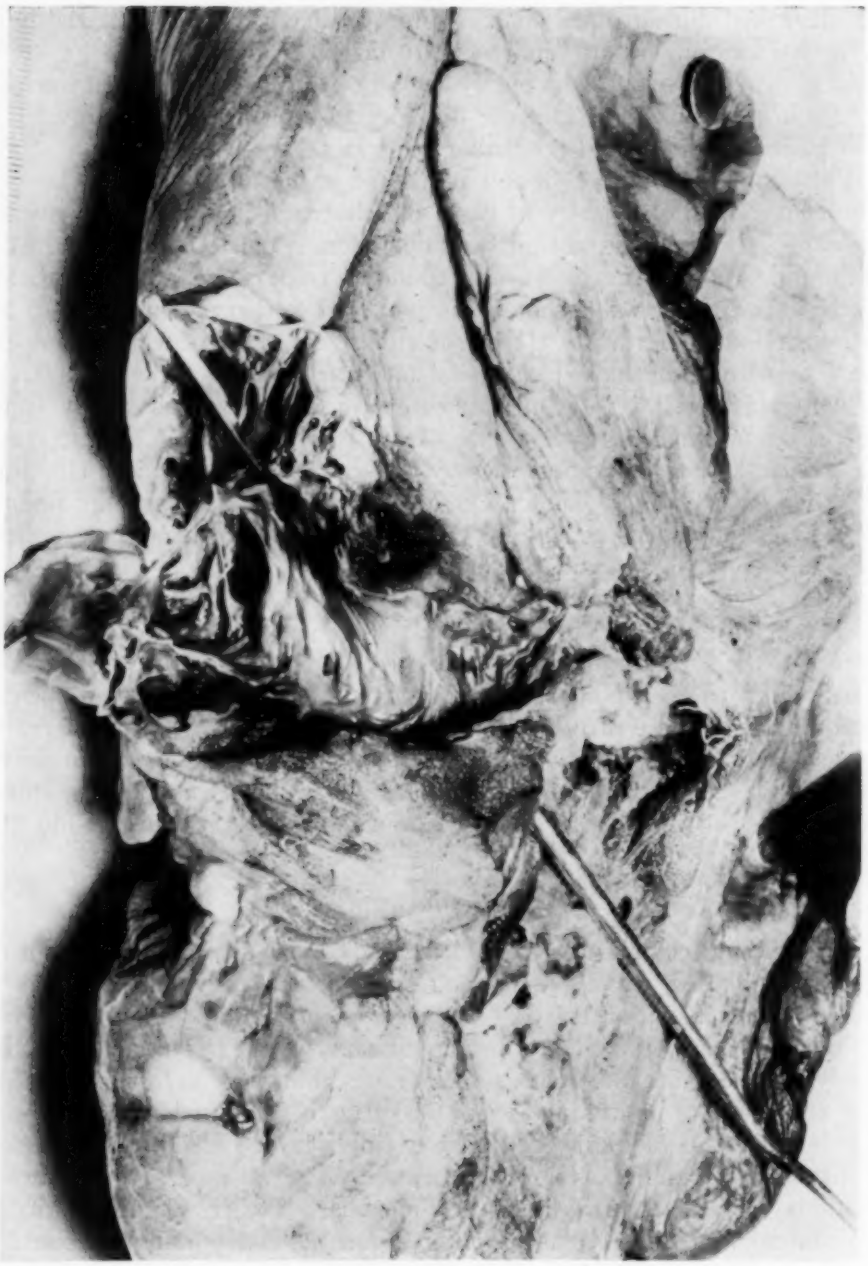

FIG. 11. *Case 2.* Specimen of the removed lung: the posterior wall of the "cavernous hemangioma" has been resected. The dilated vein and traversing trabeculae are demonstrated. The probe is within the pulmonary artery, which enters the aneurysmal cavity.

tive and elastic fibers. Numerous newly formed vascular buds suggest angioblastic activity. Arteriovenous fistulae of the lung, causing intrapulmonary tumefactions and giving rise to a now well-defined clinical complex are of particular interest in this presentation, and merit a more detailed discussion. The literature contains very few references to this subject, and

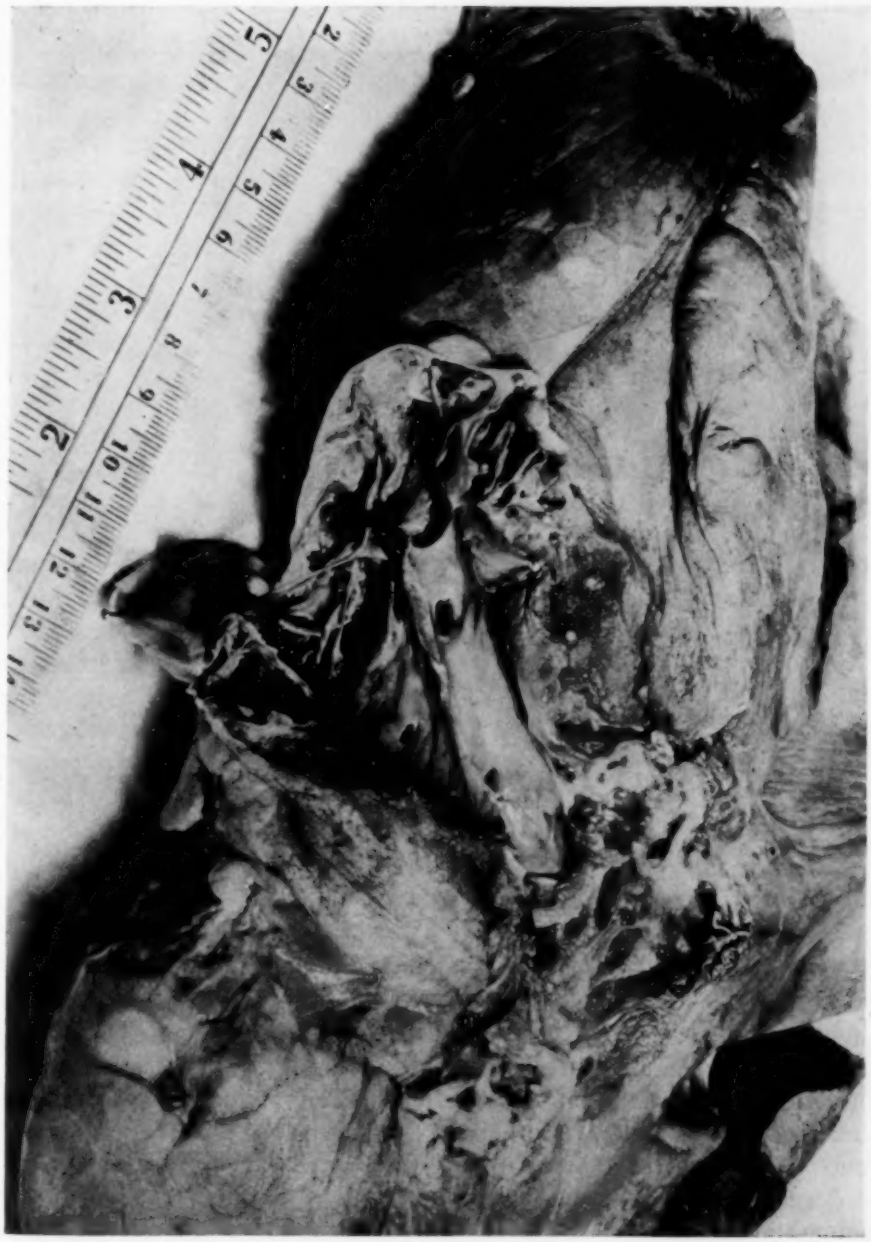

FIG. 12. *Case 2.* The pulmonary artery is opened; both sides of the fistula are demonstrated.

the pulmonary lesions which occurred either isolated or in association with the classical manifestations of hereditary telangiectases have been variously described as cavernous hemangioma, arteriovenous aneurysm or arteriovenous fistulae. The difference in terminology reflects the evolution of the concepts regarding the pathogenesis of "vascular tumors" or abnormalities as a whole.

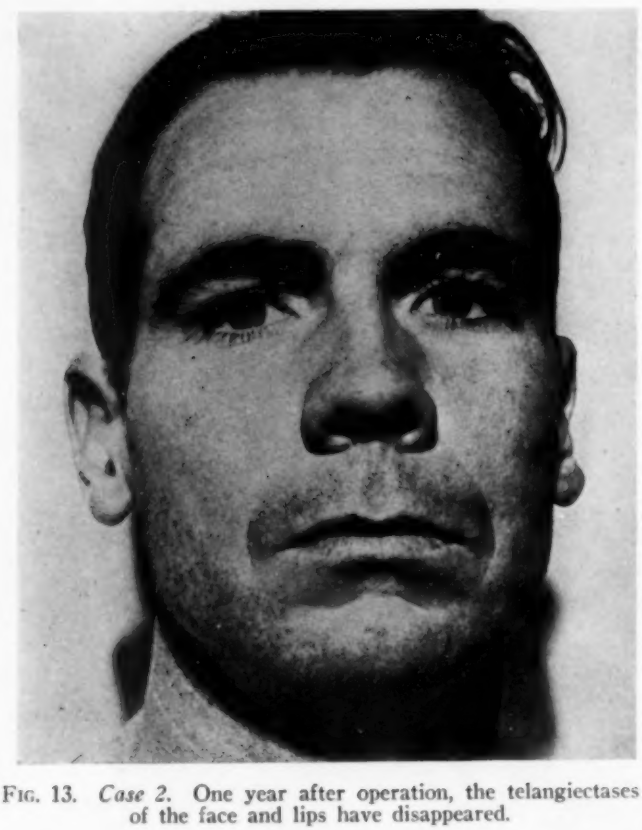

FIG. 13. *Case 2.* One year after operation, the telangiectases of the face and lips have disappeared.

Reid [38] advanced the view that cirsoid aneurysms, pulsating angiomas, and possibly simple angiomas represent essentially arteriovenous aneurysms, with abnormal arteriovenous communications. This eliminates the capillary bed, which is the normal communication between arterial and venous systems and leads to clinical symptoms depending on the size and location of the vascular abnormality. The arteriovenous communication may be either acquired or of congenital origin. The pulmonary arteriovenous fistulae so far reported and those observed by us belong obviously to the latter group. The occurrence of such congenital fistulae is readily explained by the development of arteries and veins from a common capillary plexus. Their ultimate fate is determined by the size of these communications and the pressures to which they are subjected.

The pathological alterations encountered in pulmonary arteriovenous fistulae are less familiar, and may be best described by referring to individual descriptions found in the literature. In seven of 15 reviewed cases of pulmonary arteriovenous fistulae the specimens obtained at surgery or postmortem examinations were subjected to pathological studies. The changes consisted uniformly of a distended afferent artery and distended efferent veins. Between the arterial and venous systems there is either a direct communication through one or several larger vascular trunks, or a tangle of more or less distended vessels instead of capillaries. Owing to the fact that the arterial pressure is transmitted directly into the malformed vessels and into the veins, these become increasingly dilated. Degenerative changes arise in the walls and in some cases ruptures occur. Because of these, new pathological communications may arise between the vessels, which increase the circulatory disturbance still further. Ruptures of vessels may also give rise to hemorrhages in surrounding areas. In the case of Jones and Thompson [21] there were also other anomalies; the middle lobe was absent. The right upper lobe had many blue, thin-walled "varicosities" over its anterior surface, and there appeared to be a very thin-walled sac filled with dark blood projecting from the lower aspect of the upper lobe at the site corresponding to where the middle lobe should have been. There were communications between the multilocular hemangiomatous cavities, the superficial varicosities, and the inferior pulmonary vein. The superior pulmonary vein was absent. Microscopically, the cavities are usually lined by mesothelial cells lying on a fibrous connective tissue wall.

Pathological studies of the specimen obtained from our patient (case 2) showed a large thin-walled vascular sac in the posterior portion of the right lower lobe near the apex, containing approximately 22 c.c. of blood. Three other similar sacs, measuring less than 1 cm. in diameter, were scattered within the lower lobe, projecting partly on the pleural surface of the lung. The right upper lobe contained two similar lesions and one was observed in the middle lobe. On dissection, the large arteriovenous fistula in the lower lobe was composed of two arteries, a dilated sac and the inferior pulmonary vein. The sac interposed between the communicating vessels was divided into multiple locules by fibrous strands traversing the cavity. Communicating vessels could also be demonstrated in all other fistulae. The small cavities resemble a large sinusoidal or cavernous network. The histological changes conformed essentially with those described in other cases.*

On the basis of our observations it seems justified to assume that congenital arteriovenous pulmonary fistulae result from a gross deviation of capillary formation, and appear as single or multiple lesions, quite frequently associated with hereditary telangiectases. We should, therefore, prefer to reject the term of "varicosities" as applied to this disease.

*We wish to express our appreciation to Lt. Col. Robert W. Holmes for the pathological studies of the specimen.

Radiological Aspect

Pulmonary arteriovenous fistulae, or cavernous hemangiomata, thus far reported in the literature, present sufficiently characteristic features to permit a definition of radiologic diagnostic criteria. They have been adequately described by Lindgren,[25] and our own cases confirm his observations.

In all cases circumscribed, slightly lobulated shadows of increased density were observed in the lung. Occasionally the lesions were multiple and bilateral. The intrapulmonary opacities were connected with the hilar vessels by broad, tortuous bands of increased density, representing a distended branch of the pulmonary artery and a dilated pulmonary vein, both of which opened into a tumor-like vascular sac. Usually two such vessels were observed, but in some instances more anomalous vessels were encountered. The communicating vessels lie in different planes, and it is usually necessary to obtain films in several projections to demonstrate the anatomical relations of the abnormal vessels and the tumor, produced by this abnormality. Fluoroscopic examination may reveal pulsations of the tumor. The tumor may show variations in size, depending on change of the intrathoracic pressure. On Valsalva test (deep inspiration, followed by forced expiration against the closed glottis) the mass may become smaller. Mueller's test (deep expiration, followed by forced inspiration against the closed glottis) causes an increase of the mass. The variations in size may be difficult to observe since the change is not very marked. The significance of pulsations of tumors must be carefully evaluated. It is rather difficult to differentiate definitely between spontaneous and transmitted pulsations, particularly when a tumor is located near the hilum, and only a part of the circumference of the tumor can be demonstrated. The pulsation of peripherally located lesions can be proved more readily by appropriate kymographic studies.

Lindgren [25] stressed the importance of careful studies of the pulmonary vessels and their relation to a pulmonary tumor. This, in his opinion, is the most reliable criterion, permitting a correct radiologic diagnosis. Even small arteriovenous fistulae show at least two vessels, connecting them with the hilar vessels. These vessels are larger than other vessels in the same region and follow a different course. The more peripherally located tumor can not be separated from the apparently abnormal vessels.

The radiologic diagnosis may be quite difficult. Small cysts, adenomata, metastatic lesions and tuberculomata are only some of the lesions which may offer differential problems. Aneurysms of the branches of the pulmonary artery may also cause round opacities, simulating other lesions. Lindgren [25] points out that they should be distinguished from other changes by the demonstrable vascular origin of the opacity and from the arteriovenous fistula by the fact that in the latter, the vessels are more distended, and at least two can usually be demonstrated. It is also well to remember that an aneurysm of the pulmonary artery without a shunt does not cause cyanosis, which is an important symptom in cases of arteriovenous fistulae.

Intrapulmonary hemorrhages resulting from a rupture of the dilated vessel cause occasionally irregular densities, and even segmental atelectases, obscuring the primary lesion, and thereby add to the diagnostic difficulties. There, too, careful observation of anomalous vascular bands adjacent to the irregular densities aids materially in arriving at a correct diagnosis.

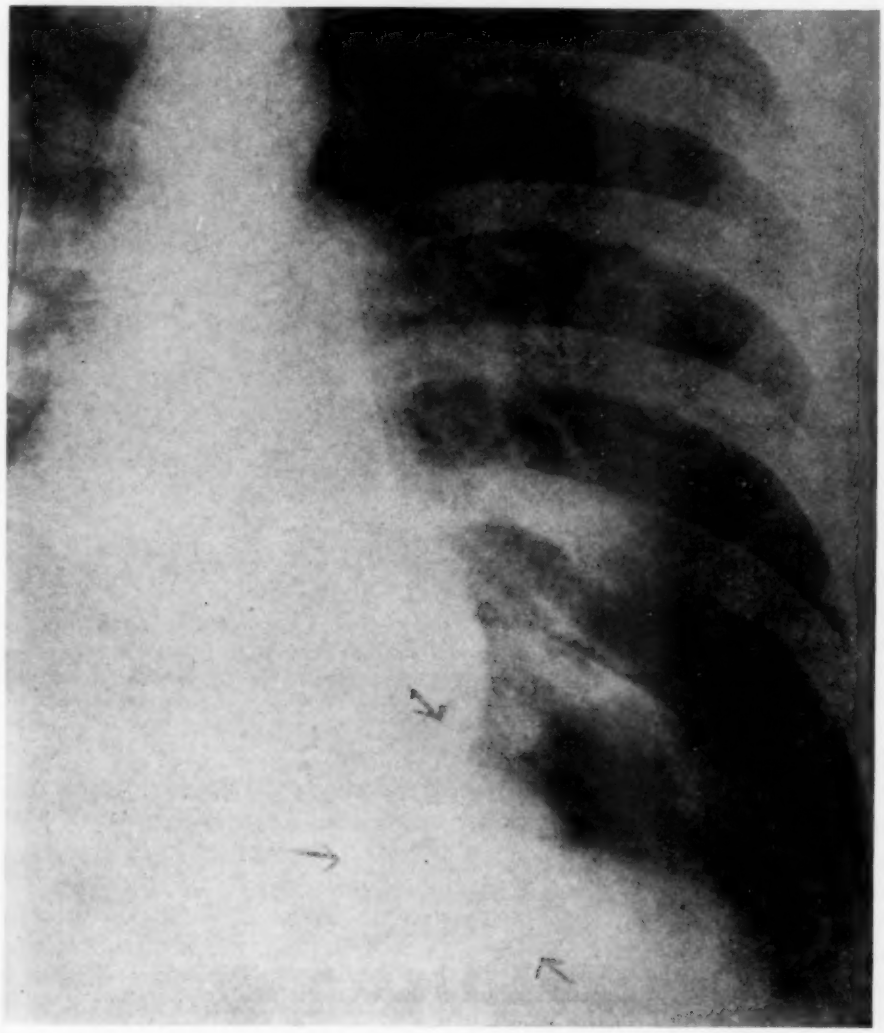

FIG. 14. *Case 3.* PA roentgenogram of the chest showing two round opacities at the left base, representing pulmonary "hemangiomata."

The lack of cardiac enlargement mentioned previously is rather conspicuous in cases of pulmonary arteriovenous fistulae. This is in striking contrast to the arteriovenous fistulae in the greater circulation, and most likely contributes to the diagnostic difficulties from the radiologic point of view when the clinical history is not available.

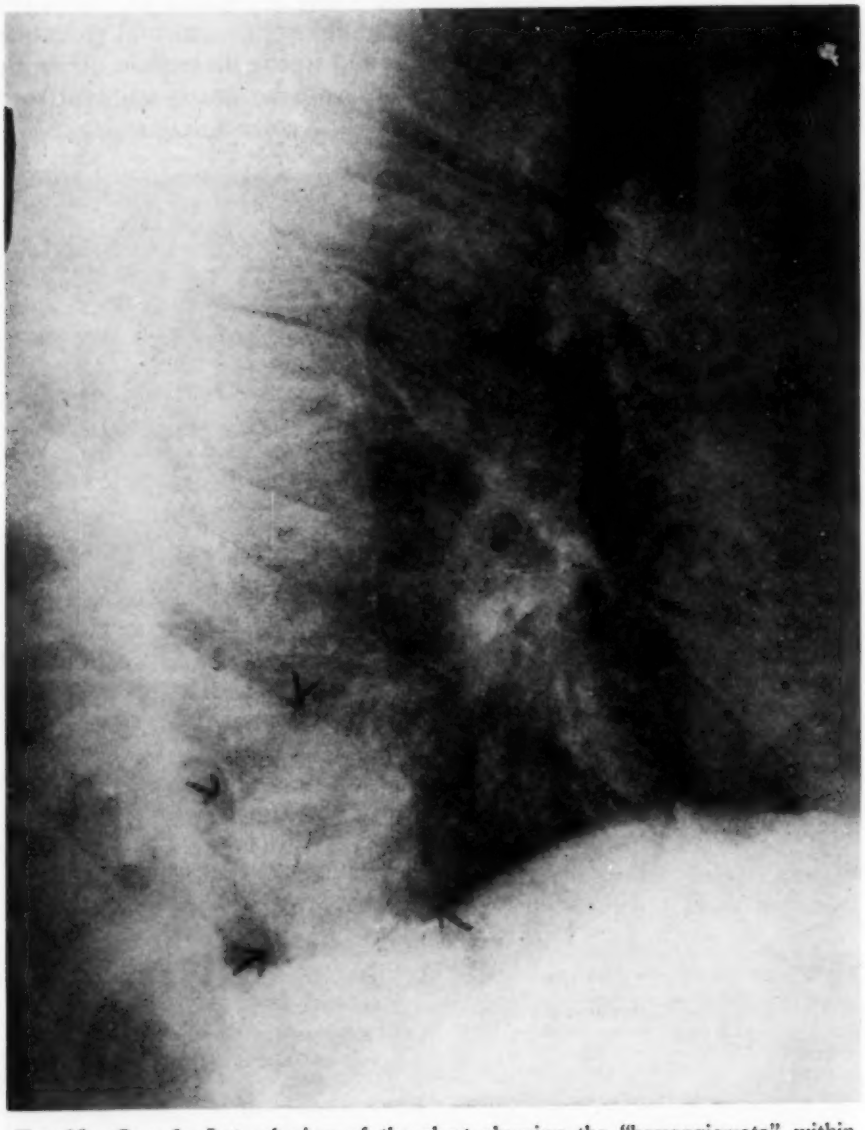

FIG. 15. *Case 3.* Lateral view of the chest showing the "hemangiomata" within the dorsal segment of the left lower lobe.

The routine radiologic examination can be advantageously supplemented by body-section radiography and angiography. The planigrams of the case reported by Jones and Thompson [21] demonstrated very clearly a multilobulated mass arising from the branches of the right pulmonary artery. The connecting branches were markedly dilated and their course was abnormal.

Angiography, when successful, demonstrates clearly the vascular character of the tumor, and its connection with the pulmonary vessels. Intravenous injection of 70 per cent Diodrast seems to be preferable to introduc-

tion of the dye after catheterization, because of suggested greater inherent danger in the latter method. It should be emphasized that special caution must be exercised in the use of angiography in cases of arteriovenous fistulae. Among other dangers, the possibility of thrombosis must be kept in mind. The high cell volume, associated with this disease, makes the possibility of thrombosis very real. Congenital pulmonary arteriovenous fistulae are not always single lesions. On the contrary, the evidence now at hand indicates that they are perhaps more frequently multiple, and may occur in both lungs. The lesions demonstrated radiologically represent usually the largest fistulae in a given case, but by no means the only one. In addition, there may be several or even numerous small "cavernous hemangiomata," located underneath the visceral pleura, producing small irregular prominences on the pleural surface of the lung, but not extending appreciably into the pulmonary parenchyma.

It is not at all surprising that small sub-pleural "hemangiomata," in close contact with the structures of the thoracic cage, escape radiologic detection on routine examination. The lack of the essential contrast of densities accounts for this. It may be necessary, at times, to include a diagnostic pneumothorax as an additional procedure to those already discussed. It is essential to obtain several films, in various projections, in order to demonstrate the pleural surface of the lung, along most of its circumference. A better visualization of the "hemangiomata" can be obtained on deep inspiration followed by forced expiration against the closed glottis (Valsalva test), and the exposures should be preferably made under those conditions.

The pulmonary lesions may occasionally be associated with hypertrophic osteoarthropathy, as seen in congenital heart diseases or chronic pulmonary diseases. The skeleton in our cases was normal.

Treatment

Certain observations appear pertinent in relation to the treatment of pulmonary arteriovenous fistulae. As we mentioned previously the clinical manifestations of the disease depend on the size of the shunt within the pulmonary circulation. Small fistulae, usually asymptomatic, may require no treatment at all. It is advisable, however, to observe those patients over prolonged periods of time, since existing fistulae may increase in size, and others may become manifest either in the already involved or in the contralateral lung. Serial roentgenograms will in such cases reveal the evolution of these lesions. Repeated blood counts may prove an adequate indicator of the progress of the disease, reflected in the secondary polycythemia.

Symptomatic arteriovenous fistulae necessitate surgical intervention. Total pneumonectomy, lobectomy or partial resection of a lobe have been performed, depending on the findings ascertained on thoracotomy of individual cases. Of eight patients subjected to surgery, three had a total pneumonectomy. In Jones'[21] case there was no superior pulmonary vein; in

Adams' [1] case multiple lesions involved more than one lobe; and in Shenstone's case there were such large vessels around the hilum that pneumonectomy was deemed necessary. Pennoyer [35] emphasized a similarly increased vascularity in the region of peripheral arteriovenous fistulae as a characteristic feature of the disease. Lobectomy was performed in two cases. In two cases, the operation was limited to local resection of the lesions.[20, 25] Janes [20] resected locally two lesions, one of which was present in each lower lobe. In one case the operation was limited to lingulectomy.[25]

Venous thrombosis deserves consideration in the management of these cases because of the marked polycythemia and increased blood viscosity. Although anticoagulants were not used in this case because of danger of postoperative hemorrhage, serious thought should be given to this approach in view of the postoperative complication of phlebothrombosis, which may have been prevented with dicumarol.

Phlebotomy with the withdrawal of blood replaced by plasma may also be of some value.

Summary

1. A family with hemorrhagic hereditary telangiectases has been reported and the clinical manifestations and pathogenesis of the disease reviewed.

2. Two members of this family had visceral involvement consisting of pulmonary arteriovenous fistulae.

3. The clinical and physio-pathological aspects of this complication have been discussed.

4. The pathological changes in pulmonary arteriovenous fistulae have been presented.

5. The radiologic diagnostic criteria of the disease have been described.

6. Treatment has been considered.

Addendum

Since the completion of this paper another case of hereditary hemorrhagic telangiectases complicated by an arteriovenous fistula of the lung has come under our care. The patient previously had a lobectomy elsewhere and is included here as a follow-up only.

C. S., a 28 year old white male, whose father had bleeding telangiectases of the face and frequent epistaxis, was in good health until June, 1943 when he developed telangiectases over the malar prominences and the bridge of the nose. These were accompanied by frequent epistaxis. About six months later he began to complain of night sweats, weakness and malaise without fever. The patient developed marked cyanosis associated with polycythemia and increased blood volume. Roentgenologic examination of the chest revealed two round opacities in the left lower lobe and anomalous vessels connecting these lesions with the hilar vessels. The findings were consistent with arteriovenous fistula. The left lower lobe was resected with complete relief of cyanosis, polycythemia and previous symptoms of weakness and malaise. He has remained free of symptoms to date except for bleeding telangiectases of the face and mucous membranes of the mouth and the upper respiratory tract. Laryngoscopic examination, at present admission, showed numerous telangiectases within the pharynx, larynx and trachea.

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PSEUDOHEMOPHILIA *

By Harry L. Halliwell, M.D., and Lawrence Brigham, M.D.

This report deals with a family of "bleeders" whose hemorrhagic diathesis fulfills the diagnostic criteria of "pseudohemophilia" as recently presented by Estren, Mēdal and Dameshek.[1] These authors have reviewed the literature and classified 62 patients who exhibited a tendency toward abnormal bleeding as cases of pseudohemophilia. Either sex is involved, and the striking laboratory finding is a prolonged bleeding time in the presence of normal blood platelets and normal coagulation time.

The cases presented in this report are males, five in number, ranging in age from six to 77 years. Chart 1 shows the family relationship of the five "bleeders."

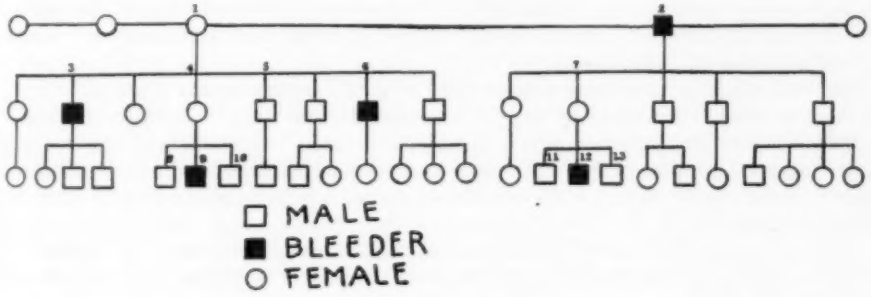

Chart 1. Only those individuals with an assigned number are discussed in the text.

Case Reports

Case 2 is a 77 year old male who had severe bleeding from minor cuts as a youth. While a youth in Europe, bleeding from minor cuts was stopped by "burning the wounds" and "tight bandages." The bleeding tendency gradually diminished in severity as he grew older. At about 50 years of age he lost all symptoms of the disease.

Case 3 is a 27 year old male. Physical examination revealed no enlargement of the spleen. Since early childhood he has experienced severe bleeding from minor lacerations. Profuse bleeding followed extraction of teeth five years ago. Patient has never been hospitalized and at present his symptoms are mild.

Case 6, brother of Case 3, is a severe bleeder and has had many hospital admissions.

First hospital admission was on June 25, 1910 at age of two years because of purulent conjunctivitis and staphyloma of the right cornea. Physical examination revealed no other abnormal findings. The right eye was enucleated. Severe hemorrhage followed the operation, but no bleeding point could be found. The operative wound was packed and bleeding stopped after 19 days.

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From the Resident Staff Pediatric Service, Rhode Island Hospital, Providence, R. I.

Second hospital admission was on March 17, 1914 for pain and swelling of the left thigh and hip of three weeks' duration. Physical examination revealed that the left hip was held in flexion and there was pain and limitation of movement. Roentgenogram of the region revealed no bony abnormality. The clinical impression was bleeding into the hip joint. No laboratory data were recorded.

Third hospital admission was for re-check of hip condition. Good function was discovered.

Fourth hospital admission was on January 26, 1940 because of a "bleeding cut" on patient's lip. Injury had occurred 10 days prior to admission. Physical examination revealed blood oozing from a mucosal tear of lower lip. A direct transfusion of 250 c.c. of whole blood was given the patient on January 27, 1940 with cessation of bleeding. Laboratory data: urine examination negative; red blood cell count 4½ million. Hemoglobin reported as 90 per cent.

Fifth hospital admission was on May 5, 1941 for a bleeding laceration of the eyelid occurring three days prior to admission. Laceration continued to ooze for three days after hospital entry before stopping. Laboratory data: Platelets normal in number. Red blood cell count 4 million; hemoglobin 14 grams; white blood cell count 10 thousand with normal differential count.

Sixth hospital admission was on May 9, 1942 because of alveolar abscess. Owing to past history of bleeding, bleeding and clotting tests were done. Coagulation time, 9 minutes by "test tube method." Bleeding time was reported as 1 minute. Method used was not recorded.

Seventh hospital admission was on June 8, 1942 for an alveolar abscess. Clotting time was normal. No bleeding time was reported. On June 9, 1942 tooth was extracted. Despite many tannic acid and adrenalin packs, silver nitrate cautery, snake venom therapy, parenteral hykinone and local thromboplastin, the tooth socket continued to bleed for 10 days. Fifteen hundred c.c. of whole blood (citrated) were used for replacement.

Admission in 1947 to a second hospital following eight weeks of oozing from dental sockets after extractions. He received a direct transfusion with cessation of bleeding.

Case 12 was a male, age 17 years.

First admission was on September 29, 1934 at four years of age for bleeding following tooth extraction. Physical examination not remarkable. Laboratory data: Urine negative; red blood count 2 million; hemoglobin 35 per cent. Platelets: many on smear. Coagulation time by three tube method was 7½ minutes. Bleeding time was three minutes. Method used was not recorded. White blood cell count was 9 thousand. Transfusion of 300 c.c. of citrated blood was given. Packings and thromboplastin were used locally. Bleeding gradually stopped after six days.

Second admission was on August 6, 1935 for alveolar abscess.

Third admission was on September 25, 1936 for bleeding about lower incisors. Teeth were removed and pressure packs used to control hemorrhage. Cessation of bleeding occurred after six to eight hours.

Fourth admission was on August 23, 1940 for hematoma and bleeding laceration of forehead of 24 hours' duration. Evacuation of organized clot in original wound with deep suturing of wound resulted in hemostasis. Discharged four days after admission.

Fifth admission was April 15, 1941 with chief complaint of swelling of left knee following traumatic injury. Physical examination revealed swollen left knee with ecchymosis on antero-medial aspect. Impression was traumatic hydrarthrosis. Roentgenogram revealed calcifications in soft tissue about knee. Knee joint was not tapped, but examination revealed fluid. On April 14 patient had a spontaneous epistaxis which ceased after two days with nasal packings. Laboratory data: Prothrombin

time 56 per cent; hemoglobin 10 grams; coagulation time by three tube method 10 minutes; bleeding time 1 minute (method used not recorded); red blood cells 4 million, white blood cells 12,000.

Sixth hospital admission was on August 22, 1941 for tenosynovitis. No laboratory data.

Seventh admission was on January 24, 1942 for bleeding hematoma of lower lip following a fall. Bleeding stopped two days after admission. He received 50 c.c. of whole blood intramuscularly. Urine examination was negative. Hemoglobin 14 grams.

Eighth admission was for swelling of the right thigh. Eight days prior to admission, patient's thigh began to swell following a slight injury. There was no known trauma to knee directly. Physical examination revealed a 10 by 5 inch ecchymotic area over the lower medial surface of the thigh which was soft and painful. The right patella floated and the knee was swollen. Discharge diagnosis was hemarthrosis of right knee. Laboratory data: Red blood count 4.16; white blood count 15.8; hemoglobin 11.5 grams. Roentgenogram of the knee revealed no bony abnormality.

Ninth hospital admission was for removal of teeth on September 24, 1946. Physical examination revealed dental caries and an ecchymotic area over the right shin. Bleeding time done at this time by Duke method was 5 minutes. Following removal of two teeth, patient bled profusely for four days. An immediate postoperative transfusion of 500 c.c. of whole citrated blood was given. On September 29 a transfusion of 500 c.c. of citrated blood was given because of continued blood loss. On September 30 patient received 25 c.c. of whole blood directly and bleeding stopped for 18 hours. Bleeding began again despite topical thrombin, oxycel and gauze packs. On October 1 a direct transfusion of 140 c.c. of blood resulted in cessation of bleeding abruptly for 24 hours. Tooth sockets began to ooze slightly at that time but packing with tannic acid checked further ooze. On October 3 prothrombin activity was 75 per cent of normal. On October 8 patient received 500 c.c. of whole citrated blood for replacement purpose. Laboratory data on October 7: Red blood count 3.5; hemoglobin 12.3; coagulation time by three tube method 9 minutes; bleeding time by Duke method 4.5 minutes.

Case 9 is a male, age six years.

First hospital admission was on July 1946 for an oozing laceration on the right buttock sustained eight days prior to admission. Physical examination revealed dental caries, hypertrophied tonsils and two ecchymotic areas over lower back. A two-inch oozing laceration was evident on the right buttock. Patient gave a history of abnormally easy bruising. Laboratory data on admission before any transfusion revealed clotting time of 10 minutes with normal clot retraction. Prothrombin time was 70 per cent of normal. Red blood count was 3 million; hemoglobin 9.7; white blood count 11.9. No bleeding time was recorded. Bleeding continued despite many local measures and red blood cell count fell to 2.1 and hemoglobin to 7 grams on July 19. On July 20, 700 c.c. of whole citrated blood were given. On July 22 patient was brought to operating room and wound was packed with oxycel and deep sutures inserted. Postoperatively bleeding ceased. On July 31, 1946 clotting time by three tube method was 11 minutes and bleeding time 5 minutes.

Second hospital admission was on April 23, 1947 for a bleeding laceration of left forehead. Pressure dressing appeared to stop bleeding and patient was discharged two days after admission.

Third hospital admission was on April 27, 1947 for bleeding laceration for which patient had been admitted four days previously. Laboratory data on admission: Red blood count 4.1; hemoglobin 11.6; clot retraction normal; clotting time 2½ minutes by one tube method; bleeding time by Duke method greater than 15 minutes. On April 30 patient received 250 c.c. of blood, and a tight pressure dressing resulted in ces-

sation of bleeding for 24 hours. Because of persistent oozing, patient was brought to operating room on May 1 for suturing of wound. He received 250 c.c. of fresh citrated blood on this date. On May 3, 1946 red blood cell count was 3.9; hemoglobin 12; platelets plentiful on blood smear. Laceration was still bleeding. Wound was packed with gauze in an attempt to stop bleeding. On May 4 bleeding stopped. On May 12 bleeding time was greater than 15 minutes; clotting time 7 minutes; tourniquet test negative; platelet count 220,000. On May 21 patient was brought to operating room where gauze packing was removed. Patient received 130 c.c. of whole blood by direct transfusion before the surgical procedure. Granulation tissue was cut away without any abnormal bleeding. Nineteen hours postoperatively bleeding time was 6 minutes. Sixty-seven hours after operation, at time of discharge, bleeding time had lengthened to 8.5 minutes.

Autopsy Reports

The cause of the deaths of Cases 8 and 11 cannot definitely be decided. Brief summaries of the autopsy findings follow. It will be noted that both cases showed pathological hemorrhages at postmortem examination.

Case 8, a male, was stillborn on April 18, 1935. Weight was 10.5 pounds. Delivery was by a breech extraction. The right adrenal was completely destroyed by hemorrhage.

Case 11, a male, was born on May 28, 1939 by breech delivery. Shortly after birth, rapid ecchymosis appeared in the right hand and both feet. On May 29 patient died after experiencing some respiratory difficulty. Multiple hemorrhagic extravasations were found within the skull, spleen and in various locations in the soft tissues of neck and trunk. Multiple petechiae in the heart (subpericardially) and in the skin of the upper and lower extremities were noted. A persistence of fetal type of blood circulation was present.

Laboratory Findings

Hematological studies of Cases 2, 3, 6, 9, and 12, all clinical bleeders, revealed normal values for red blood cell count, hemoglobin and white blood cell count. Blood smears showed normal white blood cells and normal differential counts as well as no diminution in platelets. During his first hospital admission, Case 12 had a red blood cell count of 1.9 million and a hemoglobin of 5 grams which was the result of blood loss. The severity of this blood loss resulting from small oozing lacerations or tooth extractions is emphasized by the fact that Case 6 received 1500 c.c. of blood during his sixth hospital admission; Case 9, 1200 c.c. during his first hospital stay; and Case 12, 1700 c.c. during his ninth hospital admission. At the time of this study no individuals showed anemia secondary to chronic blood loss.

Table I

May 1947

Case	Coagulation Times
2	7 minutes
3	8
6	5½
9	7
12	4½

Coagulation Time. The determination of coagulation time was according to the Lee-White three tube method. Normal values accepted were between two and 10 minutes.[2]

Table 1 records the values obtained—all within normal limits.

Bleeding Time. The Duke method was used, in which a small cut was made on the volar surface of a digit. The cut was deep enough to cause oozing without pressure. At intervals of 30 seconds the drops of blood were removed by means of a blotter without touching the skin. According to Wintrobe,[2] a bleeding time greater than five minutes should be considered abnormal. Normal controls [14] for this method ranged from 2 to 4.5 minutes. Only those bleeding times considered valid during past hospital admissions are included in the table below. All but Case 2 showed a definitely abnormal bleeding time.

TABLE II

Bleeding Times

	During Past Hospital Admissions			During Present Study				
	7-31-46	9-24-46	10-7-46	4-30-47	5-12-47	5-22-47	5-25-47	6-9-47
Case 2					4			2½
3					7½			
6					>15			
9	5			>15	>15	6	8½	
12		5	4½	7½	5½			

The platelet counts on all five cases were normal. Blood smears also indicated platelets to be plentiful.

TABLE III

Case	Platelet Count
2	200,000
3	250,000
6	200,000
9	220,000
12	280,000

All platelet counts were well above the value that would result in abnormal bleeding.

Prothrombin activities on all cases were within normal limits during the present study. Method used was a modified Quick method based on controls.

TABLE IV

Prothrombin Activity Expressed as Per Cent of Normal Past Hospital Admissions May 1947

	4-14-41	7-19-46	
Case 2			100%
3			150
6			150
9		70%	90
12	56%		90

Tourniquet tests were carried out in the following manner. A blood pressure cuff was maintained half way between systolic and diastolic pressures for 15 minutes, and the petechiae were counted in a circle one-inch in diameter on the flexor surface of the forearm. More than 10 new petechiae were considered a positive test. Only Case 2, the 77-year-old individual, showed a positive test. Examination of his fundi revealed marked arteriosclerotic retinopathy.

Serum calcium determinations were done on Cases 6 and 12. The value for both was 9.4 mg. per cent.

Clot retraction began within one hour and was completed well within 24 hours in all cases.

The following table contains the results of tests carried out on relatives of the five clinical "bleeders." The exact family relationship may be found by referring to chart 1.

May 1947

	Coagulation Time	Clot Retraction	Bleeding Time	Platelet Count	Tourniquet Test	Prothrombin Activity
Case 1	7½ minutes	Normal	5 minutes	—	—	
4	4 minutes	Normal	3½ minutes	230,000	Negative	120% of normal
5	4½ minutes	Normal	4 minutes	—	—	
7	3½ minutes	Normal	2½ minutes	188,000	Negative	
10	6 minutes	Normal	7½ minutes	530,000	Negative	120%
13	3½ minutes	Normal	4½ minutes	142,000	Negative	160%

It is of interest to note that Case 10 had a definite prolongation of bleeding time. This case is a male, age 9, brother of Case 9, a severe bleeder. He has exhibited no abnormal bleeding.

Discussion

The symptoms exhibited by these five cases include excessive bleeding from minor cuts, epistaxis, hemarthrosis, postoperative hemorrhage and bleeding from dental sockets after dental extractions. No history of petechiae was discovered although ecchymoses were common. As no female in this family experienced abnormal bleeding, no excessive uterine hemorrhage was encountered. Case 4 and Case 7, both mothers of males with pseudohemophilia, have undergone major operations without excessive hemorrhage.

The bleeding time was prolonged in four of the five cases with bleeding tendencies. Case 2, the 77-year-old male, who for the past 20 years had had no tendency toward abnormal hemorrhage, had a normal bleeding time. The prolongation of the bleeding time was extremely variable, at one time being greatly prolonged and at other times being slightly increased or normal. It appears that there is not a direct relationship between the severity of bleeding and the bleeding time, for on one occasion Case 12 was exhibiting severe bleeding when the bleeding time was a high normal. The coagulation time, prothrombin activity and tourniquet tests were within normal limits during present study.

The diagnosis of pseudohemophilia is not difficult. The discovery of signs of abnormal clinical bleeding in the presence of a prolonged bleeding time with normal platelets and normal coagulation time would indicate pseudohemophilia. There is commonly a family history of the disease, although this is not always present. As pointed out by Estren, Mēdal and Dameshek,[1] there is some variability in the result of the tourniquet test, prothrombin activity and clot retraction. Clot retraction and prothrombin activity are usually within normal limits. The tourniquet test was positive in 50 per cent of the cases reviewed by these authors. Either sex transmits the disease. Either male or female may be afflicted, although in this present study only males were involved. The high incidence in males and the tendency for the symptoms of bleeding to decrease with age has been described by other authors.[3, 4, 5]

Therapy. Pressure dressings, local thrombin,* thromboplastin,† calcium, vitamin C, hykinone,‡ oxycel,§ tannic acid packs, snake venom, intramuscular whole blood, citrated blood transfusions, and direct whole blood transfusion have all been used in an effort to halt bleeding. All appear to have had no effect with the exception of pressure dressings and direct whole blood transfusions. Citrated blood has had no effect in causing cessation of bleeding, but both Case 6 and Case 12 have had abrupt cessation of bleeding following direct blood transfusions. Case 9, who was under observation in the hospital during this present study, received a direct transfusion prior to debridement and removal of granulation tissue of a scalp wound which had been packed with gauze. Unfortunately, a bleeding time was not done immediately before transfusion; however, nine days previously the bleeding time was greater than 15 minutes. After transfusion, the granulation tissue about the laceration was trimmed without any abnormal bleeding. Postoperatively no hemorrhage was noted and 19 hours later the Duke bleeding time was six minutes. Owing to the tendency of these individuals to exhibit intermittent prolonged bleeding time, no definite conclusion as to the effect of the blood transfusion on the bleeding time can be drawn. Direct blood transfusions appear to have a direct effect on stopping bleeding. Fowler [5] has also found transfusion to be effective.

Summary

A family with a hemorrhagic tendency has been presented and five of its members have been classified as cases of pseudohemophilia. Case reports of these individuals and the findings of two autopsies on two other members of the family have been reported.

* Topical Thrombin, Parke Davis Co., Detroit, Michigan.
† Thromboplastin, Lederle Lab., N. Y., N. Y.
‡ Hykinone, Abbott Lab. (Vit. K Prep.), Chicago, Ill.
§ Oxycel, Parke Davis Co., Detroit, Michigan.

The outstanding laboratory finding was a prolonged bleeding time with the remainder of the findings within normal limits.

Therapeutic results with direct blood transfusions are noted as being effective in these cases.

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EXPERIMENTAL AND CLINICAL THERAPEUTIC STUDIES ON LYMPHOSARCOMA *

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Introduction

In the entire field of medicine no disorder gives so much concern to physician and layman alike as do the neoplastic diseases of the lymphoid tissue. Of this group, lymphosarcoma is a particularly serious problem. The comparatively intractable nature of the condition, its rapid progress, and the terrifying nature of the associated symptoms, all justify this concern. Especially grave is its tendency to occur in the young.

Lymphosarcoma not only presents a therapeutic problem. It also provides for the investigator particularly fascinating and useful experimental material. The tendency of the lesions to be superficial, subject to direct observation, and the invasive nature of the growth, are important features. The existence of an exact analogue in small animals, a neoplasm which can be induced and also transplanted at will, provides a unique opportunity for research directed toward therapy in man.

Finally, in both the investigative and clinical aspects of lymphosarcoma, real progress has been made. This is of a degree and type which appears to justify detailed review, since it is more apparent, perhaps, than is the case with any other form of neoplasm. Because of this fact the new knowledge concerning lymphosarcoma may well serve as a guide to what progress can be expected with cancer in general in the years to come.

A most serious error is often made in discussing the treatment of cancer. It is to describe an event following the institution of a therapeutic procedure as the result of that procedure. A conclusion of this type is never justified unless adequate data are at hand to prove that a change of the patient's course is one which is not simply a feature of the natural course of the disorder when untreated.

Particularly often in recent months have claims been made for the usefulness of one or the other substance in treating neoplasms. These claims tend to be based on minor changes in the clinical condition of the patient or in the appearance of the growth. Control observations frequently are not presented in support. Very often, indeed, careful objective studies of the day-to-day changes in the patient or in the tumor are not available during a pre-treatment period. Only when a clinical trial is under way are measurements or biopsies made. To the great surprise and gratification of the observer, periods of improvement ensue. Perhaps if the growth is biopsied areas of necrosis are seen. If biochemical measurements are made extraordinary day-to-day changes may be recorded.[1, 2]

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When the time comes to cast up accounts to evaluate these changes it is usually found that the same variations in course occur under any therapeutic régime or none at all.

With the importance of spontaneous changes of course in mind, it is well to renew the natural history of lymphosarcoma.

It would be well if every physician concerned with lymphosarcoma were to read the original description by Kundrat.[3] This is advocated because he faced the same problems of differentiating the disease from other neoplasms involving lymph nodes as are faced by every practitioner in making a differential diagnosis of a mass in neck or groin.

Further, Kundrat made the key observation which should be the cornerstone of any therapeutic attack. This was that from time to time only a single site of origin could be found. This concept of the unicentric origin is as important to the clinician as any other single consideration of lymphosarcoma.

Too frequently the true neoplastic nature of the enlarged lymph node is forgotten until control is impossible. If not forgotten, too often it is assumed to be metastatic from a primary epithelial neoplasm.

The evidence for a unicentric origin in at least some instances of lymphosarcoma is excellent, indeed unequivocal. It is found in the very substantial number of instances in which a primary focus of characteristic structure has been removed surgically or destroyed by radiologic means with complete and permanent cure.

Hellwig [4] reports that 21 of his 234 cases of malignant lymphoma showed only a single primary focus. Gall [5] reported almost the same incidence—10 per cent of 135 autopsied cases. Of 33 patients with gastrointestinal lymphosarcoma, only four could be shown to have metastasized to the regional lymph nodes. Furthermore, of 16 instances in which the regional nodes appeared to be involved on gross examination, only hyperplasia could be found on microscopic study. This observation is perhaps of particular importance since it indicates that many instances may exist in which an attempt at resection may be justified even though inspection of the tissue may suggest that extension has taken place.

These results are sometimes explained on the grounds that erroneous histologic diagnoses of lymphoid neoplasms are frequently made, due to the unsatisfactory nature of the morphologic criteria. It is difficult to believe, however, that these factors can obtain in every reported instance of cure. It is far easier and more logical to hold that the disorder does arise regularly in a single cell or cell group but often has extended before the primary locus is recognized. Any worker with transplantable lymphosarcoma in animals cannot fail to be impressed with the fact that however carefully one localizes the implanted fragment of tumor, migration to local nodes and systemic progression occur with dramatic speed.

This tendency of a disease to become systemic should not blind the observer to the possibility of localization, however. It is extraordinary how

often this is forgotten and how disastrous this may be to the patient since the really brilliant, life-saving results are obtained either by radiation or by surgery in the unicentric form of the disorder.

The age and sex distribution of lymphosarcoma has been referred to frequently in the classic publications on the subject. They deserve repetition here, however, with consideration of the possible meaning of these factors in terms of etiology of the disease.

It is interesting that in an early publication of Jackson's [6] he states that virtually no case of lymphosarcoma occurred in the first, third, fourth, or fifth decade. The report by Sugarbaker and Craver [7] describes a uniform distribution by decades and states that the disease is rare before the age of 20. It is apparent that age distribution may vary significantly with the institution involved, and unless some pains are taken to control this factor misleading figures may be obtained.

When the later figures of Jackson [8] are contrasted with similar ones pertaining to other forms of neoplasms a pronounced contrast is seen. In few other conditions is there such a sharp limitation of incidence to childhood, adolescence and late puberty. In no other does adult life almost seem to interdict the occurrence of a particular neoplasm.

Less pronounced, but very definite, is the predominance of lymphosarcoma in males.

These have been the findings of practically every investigator who has compiled statistics on the incidence of lymphosarcoma. Allowing for the minor statistical errors the disease is certainly twice as frequent in males as in females.

To draw any conclusion from these facts is, of course, impossible. One can speculate, however, and thereby derive some discussion if no decision.

It is obvious to any anatomist that a disorder which is predominant in one sex and is practically confined to childhood must have something to do with those chemicals which control sex and maturation. I refer, of course, to the substances secreted by the glands of internal secretion, the protein hormones of the pituitary and the steroids of gonads and adrenals. It is not surprising, therefore, that in certain strains of experimental animals, as shown by Gardner,[9] true neoplasms of lymphoid tissue can be caused to occur regularly by the administration of at least one steroid hormone, estradiol.

It is odd that more attention has not been given to the untreated course of lymphosarcoma. The reason is, of course, apparent; a therapeutic procedure of some effectiveness, x-radiation, was at hand before detailed knowledge of the natural progress was realized to be important. Enough observations are at hand, however, in clinics with adequate experience to suggest that the disease is not one marked wholly by an unchanging march toward fatality. Indeed, it will be seen, if objective criteria are applied, that minor variations in progress are the rule rather than the exception, though spontaneous remission is not nearly as marked a feature as it is in lymphatic leukemia.

When lymphosarcoma has progressed to the stage of widespread dissemination, so-called lympholeukosarcoma, the outlook is of course poor. Even at this stage evidence of irregular regression can be found; insofar, at least, as the size of lymph nodes, the extent of secondary manifestations and the degree of lymphocytosis are concerned.

The cause of these remissions, or periods of temporary improvement, is wholly unclear. There seems to be little doubt that some have occurred following infectious disorders of varied bacterial etiologies. Indeed, nearly every clinic has a record of at least one patient who was thought to be moribund, in whom some type of infection supervened and a dramatic, in some instances complete, though temporary, regression set in.

Obviously, when this sort of change can occur, even though rarely, in the untreated patient, its possibility must be considered when any therapeutic régime is instituted.

In a very large proportion of the patients with lymphosarcoma the disease arises primarily in lymph nodes. It is probable, according to Craver,[7] that more than 60 per cent of the patients never show evidence of an extranodal primary lesion. Where an extranodal primary lesion is present, it is almost always in the structures of the head and neck, tonsils or naso-pharynx. Most of the remaining cases are primary in the gastrointestinal tract, with rare disease in lung, bone and skin.

Surgical Therapy

Regularly, when the treatment of lymphosarcoma and of Hodgkin's disease is discussed, the fact is rediscovered or at least reannounced, that surgical resection of localized disease has cured a certain number of patients. Reference to this fact is made here only for the sake of completeness and to maintain an awareness of its existence. The possibility should be borne in mind that perhaps the predominance of disseminated lymphosarcoma may lead to the acceptance of routine radiation therapy whenever the histologic diagnosis is made. This may be done without an adequate attempt to establish the disorder as a localized one. It is conceivable, furthermore, on the basis of experimental evidence, that involvement of regional nodes accessible to removal may not rule out the possibility of surgical cure. It is interesting to note how infrequently surgery is given serious consideration even in clinics where its potential value is thoroughly understood.

The practical value of surgical therapy is best established perhaps by the figures of Hellwig.[4] Of 234 patients, he treated 130 by surgery with postoperative irradiation. A five-year survival rate of 24.6 per cent is reported. Of 21 patients with a single focus of disease so treated, 12, or over 50 per cent, were well for over five years. This is in striking contrast to the survival figure of roughly 10 per cent given for radiation therapy of all patients and an average duration of 20 months. A similar case for surgery has been made by Gall.[5]

It is interesting that in the face of this evidence, Stout [10] sees no reason to prefer surgical excision.

Radiation Therapy

This topic has been discussed so exhaustively by so many authorities of great experience, that it warrants only brief mention here. There can be no question from the evidence that cures have been obtained by this means. It is probable that some increase in the number of cures can be expected with increasing diagnostic acumen, technical skill and experience.

From the evidence at hand it appears that in the instances in which cures by radiation have been obtained, the disease has been rather well localized. This raises the question, of course, of whether surgery would not have been equally or perhaps more effective.

Palliative treatment by irradiation also is so well established as to justify little discussion. Here again one principle has been clearly defined by clinical experience. This is that the degree of palliation obtained by therapy is almost exactly a factor of the extent of disease. If it is localized to an organ, or area of well-defined extent, sufficient radiation can be delivered to the neoplastic tissue to destroy it or halt for a time its growth. If the disease is not localized or its limits cannot be defined the chances are seriously against any profound or prolonged effect of therapy. This simple concept brings the treatment of lymphosarcoma directly in line with that of other neoplasms but with two points of difference. Lymphoid disease has a greater tendency to disseminate early and has a much greater sensitivity to radiation. For the latter reason the possibility of cure by x-rays of deep-seated disease should be distinctly greater for lymphosarcoma than for neoplasms of other tissues. This presumption is probably supported by the clinical results.

Sugarbaker and Craver [7] report a five year survival rate of all cases treated at the Memorial Hospital of 15.9 per cent, and apparent cures 10.6 per cent. This compares well with the figures published from other clinics using radiation therapeutically.

An interesting point in a consideration of end results is the fact that the giant follicle lymphomas show an average survival rate of 42 months, whereas the patients with malignant lymphocytoma survive an average of 18.6 months.

It is important to note that of the 21 patients surviving only four had two contiguous areas of involved tissue when first seen. This bears out the contention specified previously, that local disease is curable and generalized disease is not.

Age plays an important rôle in prognosis. Of Sugarbaker's [7] series, only one patient under the age of 30 survived, and the life expectancy in this group was half that among older patients.

Treatment by P^{32}

The announcement by Lawrence [11] of the use of radioactive phosphorus in the treatment of leukemia was a dramatic one. It stimulated immediately hope that by the use of this isotope control or cure of lymphosarcoma could be obtained. The study by Marinelli [12] of the physical basis of dosimetry in radiation therapy should be consulted on this point. Without perusal of this erudite work, however, a simple examination of the evidence gives reason for skepticism. The figures published by Lawrence [13] for the preferential deposition of P^{32} in lymphomatous as compared to normal tissue of a similar type are important. The neoplastic cells were found to contain only from two to three times, rarely more, of the isotope than did normal cells. P^{32} is an emitter of gamma radiation of great penetrating power, hence the destructive effects penetrate a considerable distance. The dose of gamma rays required to destroy the cells of lymphosarcoma is well known. From these facts it is clear that it would be unlikely that one could obtain, with a preferential deposition as low as 2 or 3 to 1, curative concentrations of P^{32} in the cells of lymphoma without a serious hazard of ruin to the normal hematopoietic tissues.

Actual experience has borne out this assumption, although it must be said that the publication of Kenney and Craver [14] presents surprisingly good evidence of temporary remission in some instances following P^{32} therapy of lymphosarcoma. Whereas sometimes similar results have been attained in other hands, one is impressed by their rarity. Warren,[15] Reinhard,[16] and many others support the conclusion that P^{32} is not a useful agent in the treatment of lymphosarcoma and, further, that its employment is associated with an unpredictable hazard.

The possibility of treatment of lymphosarcoma by some form of isotope therapy in the future cannot be ruled out. We know, now, from experience with cancer of the thyroid gland, that preferential deposition of radioactive isotopes in neoplastic as compared to normal tissue may have to attain levels of 50 to 1 or more to effect control of the growth. To do this for lymphosarcoma will require some radically new approach.

Treatment with HN2

The extraordinary development of war research which led to a knowledge of the leukotoxic action of the nitrogen mustards represents a landmark in therapeutic approach to neoplastic disease. This statement should not be taken to imply that the β-chloroethylamines are in any sense curative, or indeed that they have any value in treatment beyond the transient and irregular control of neoplasms of the hematopoietic system. Even this control, however, may be a matter of the greatest importance. It establishes beyond question the fact that a chemical treatment of one form of neoplastic disease exists, poor and incomplete though this may be. It is hard to believe that

some modification of the molecule already known to be active will not lead to more effective compounds in the future.

The facts regarding nitrogen mustard can be easily summarized. These compounds are characterized by the presence in their molecule of a β-chloroethyl group. This group in the blood becomes temporarily cyclicized to an imine ring which has, while it exists, a profound leukotoxic activity. The effect is exerted on all hematopoietic tissue including the lymphoid, and is associated with a series of toxic side reactions which may be serious or indeed fatal. Neoplastic cells of origin from hematopoietic tissue share, with their parent normal cells, sensitivity to the toxic effects of the mustard compounds. From the available evidence, indeed, certain neoplastic cells may exceed their normal relatives in sensitivity to these compounds.

The first proof that a nitrogen mustard could be employed effectively in the treatment of lymphoma was advanced by Gilman [17] and his associates. Soon after, Jacobson [18] described pronounced effects upon Hodgkin's disease. Since that time very extensive observations from many clinics have been reported in a number of publications. It suffices to state here that the treatment of lymphosarcoma by the nitrogen mustards has not been very satisfactory. In occasional and unpredictable instances dramatic regressions result. It is safe to state that these are so transient in most cases that the distress caused by the treatment is hardly justified by the benefit obtained. Unfortunately for the rule, however, an occasional patient with generalized lympholeukosarcoma is seen whose improvement is not only impressive but also is of long duration.

It is obvious from what has been said before that localized lymphoid disease is wholly unsuitable for treatment by nitrogen mustard. Only x-rays or surgery should be used. Whereas the chemical can be tried in cases of generalized lymphosarcoma it probably offers little more, if as much as, x-ray therapy. If other means have failed, however, there can be little question but that an adequate course of nitrogen mustard therapy is wholly indicated, and may be transiently life-saving.

Miscellaneous Therapeutic Procedures Not Established but under Study

Colchicine has been eyed for years as an agent of potential usefulness in the treatment of neoplasms of various types, including lymphosarcoma. The strong effect of this substance in stopping mitosis provides good reason for consideration of its use in restraining growths characterized by more rapid cell division than normal. The fact should be recalled that this is not necessarily true of neoplasms. To date no adequate data exist to justify the clinical use of colchicine or compounds allied to it.

Hahn [19] and his associates have described the preparation and have referred to the use of colloids of radioactive gold and of manganese. The

distribution of the radioactivity resulting from the injection of these materials has been described.

It is entirely reasonable to assume from the data presented by these investigators that a substantial part of the administered colloid is deposited, together with its radioactivity, in phagocytic cells. It is further probable that it remains for a time at least in those phagocytic cells which are in immediate contact with the circulation, the cells of the reticulo-endothelial system. The prominence of this system in those tissues which are subject to invasion by lymphosarcoma renders understandable the assumption that a radioactive element deposited in it would be therapeutically active. This is of course wholly possible, but hardly seems probable. The distribution of phagocytic endothelium is most widespread, particularly so in tissues of vital importance to life and composed of hematopoietic cells which are most sensitive to radiation.

No evidence has been advanced, so far, to warrant the conclusion that radioactive colloids can be controlled sufficiently well in their distribution in the body to be specifically destructive to neoplastic cells.

The discovery by Paterson [20] and her associates of the therapeutic effect of urethane in the treatment of leukemia has aroused much attention. This outstanding work is an example of a model program of medical study. There can be no doubt from the evidence that urethane, in adequate doses, has a distinctly inhibitory effect upon the growth of certain types of neoplastic cells. A particular advantage of this compound is, of course, the fact that the material is active by mouth.

A number of articles have appeared on the use of urethane in the treatment of leukemia, and one [21] which indicates an effect on cancer of the prostate gland. Whereas attempts have been made to control lymphosarcoma the results have been at best equivocal and at worst unsatisfactory. No proof exists today, in published form, which warrants the belief that urethane or any analogous compound so far prepared is of even potential utility in the control of lymphosarcoma.

An important development has been the study by Shear [22] and his associates of the use of polysaccharide from *Serratia marcescens* culture filtrate. This is, of course, a development of the earlier study by Coley and others of the effect on malignant tumors of a vaccine composed of a mixture of *Streptococcus erysipelatis* and *B. prodigiosus*. This extremely interesting and important study has advanced clear evidence that the polysaccharide has a profound effect in inducing hemorrhage in transplanted tumors and inducing a variable degree of necrosis in spontaneous ones. The pyrogenic effect of the material has been a handicap as far as its general use in man is concerned. It is hoped that studies now in progress will be useful in solving this problem.

The report of Brues and Shear [22] refers to the treatment of one patient with lymphosarcoma by polysaccharide and records are available on others. In Brues' patient several enlarged lymph nodes remote from the site of recent

x-ray therapy were seen to regress and one of the remaining tumors had developed a hemorrhage.

In any general discussion of lymphosarcoma and its therapy some view of the future must be taken. This must include very obviously a consideration of experimental work now in progress or visualized for the near future.

A matter of interest is the study of Kopac.[23] This investigator has employed a complex and delicate physico-chemical procedure to detect substances of potential value to tumor chemotherapy. Observations made by this procedure led in part to the employment of stilbamidine in the treatment of myeloma. No data on its use in lymphosarcoma have appeared so far.

Two studies have been published which suggest that 11-dehydro-17-hydroxycorticosterone (Compound E) have an effect in restraining the growth rate of lymphosarcoma in experimental animals. The observation of Heilman and Kendall [24] was that by the use of this material implantation of a strain of highly malignant tumor cells did not result in the growth of tumors and rapid regression of well developed tumors took place. Considerable variation in the experimental results was observed.

Somewhat similar results were reported by Murphy and Sturm [25a, b] who employed a transplantable tumor of the rat which, depending on the route of inoculation, may present either a lymphosarcoma or leukemia. It is unfortunate that such small amounts of compound E are available as to make large scale repetition of these experimental results not feasible.

The field of anti-vitamins and anti-hormones has been given careful consideration by those interested in the therapy of lymphosarcoma. Only one publication bearing on this area of work has been reported, however. Stoerck [26] has described a failure of a transplantable lymphosarcoma to take in animals deprived of pyridoxine. Further, he was able to cause regression of established transplants of the tumor by administering a pyridoxine antagonist. Further results of this type will be awaited with great interest. Although adequate data are not available today they may be expected in the near future in light of the numerous studies now in progress.

The treatment of lymphosarcoma presents today a curious anomaly. This most radio-sensitive tumor shows, nevertheless, resistance to control by x-radiation in terms of substantial cure rates or prolongation of life. The cells of this neoplasm are so sensitive to a change of environment that almost alone, of all new growths, they cannot be grown in tissue culture or upon the chorioallantoic membrane of the chick. Yet in man they are amazingly resistant to injurious chemicals.

Happily, however, accurate experimental technics have now been developed and are in extensive employment. A number of chemical compounds are at hand which injure lymphosarcoma cells in animals and with some degree of preferential specificity.

It would be remarkable if, in view of the effort now under way, major progress were not made in the future.

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ABNORMAL RAPID RHYTHMS ASSOCIATED WITH DIGITOXIN THERAPY *

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SEVEN patients developed abnormal rapid cardiac rhythms (idio-ventricular rhythms, paroxysmal ventricular tachycardia or interference and dissociation) during a recent fifteen and one-half month experience with digitoxin at the Peter Bent Brigham Hospital. Because they seemed more frequent and insidious than with digitalis leaf the incidence and manner of these toxic reactions were studied in this group and in a comparable group which had received digitalis leaf.

From February 1, 1943 through May 31, 1945 inclusive, 5,082 patients were treated in the Medical Service. Of this group, 940 (or 18.5 per cent) had heart disease. In the vast majority (15.5 per cent) the cardiac condition was the reason for the patient's hospitalization, whereas in a small group (3.0 per cent) the cardiac condition was of secondary importance and not the actual occasion for the patient's hospitalization. Of this group of 940 cardiacs, 534 patients (56.5 per cent of the cardiacs or 10.5 per cent of all medical admissions) were treated with pills of the powdered digitalis leaf. Most of these treated cardiacs (6 per cent of the entire group) received digitalis in "priming" digitalizing doses, while a smaller number (4.5 per cent) were given maintenance doses only, usually one tenth of a gram daily.

During this "digitalis leaf period," although 15 patients had abnormal rhythms of the type under discussion (six paroxysmal ventricular tachycardia, five paroxysmal nodal (?) tachycardia, two paroxysmal tachycardia of undetermined type, and two idioventricular rhythms) 10 occurred in patients not receiving digitalis and there were only two in which the tachycardia could certainly be attributed to digitalis intoxication. One was a 47 year old negress with malignant hypertension, uremia, and pulmonary embolism who had been on maintenance doses of digitalis leaf and then developed an idioventricular rhythm (rate 110) when given 0.1 gram digitalis leaf daily for 18 days. The other was a 62 year old man with idioventricular rhythm (rate 136) to whom digitalis had been given in rather large doses (0.7 gram of the leaf in two days) after being on maintenance doses of digitalis leaf for months in face of desperate, grave congestive heart failure. In three additional cases (two paroxysmal ventricular tachycardia and one atypical paroxysmal tachycardia), although the patients had received digitalis, the rôle of digitalis in the inception of these rapid rhythms was very

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questionable. However, for the sake of the argument, all five of these cases are here considered as due to digitalis intoxication.

From January 1, 1946 through April 15, 1947, on the other hand, when a large scale clinical trial of digitoxin had been begun, there were 2,816 medical admissions. During this "digitoxin period" 338 patients (12 per cent of the medical admissions) received digitoxin in therapeutic or therapeutic plus maintenance dosage. During that period, seven cases of toxic rapid action of the heart were encountered. The attending resident and visiting physicians, under whose direction the drugs were given, were essentially the same in each period and the same degree of care and caution was exercised in the administration of each preparation. Most of the subjects, being hospital patients, had severe or moderately severe congestive heart failure, else, particularly at this time, they would not have been hospitalized. One might question whether a group of non-hospitalized patients in milder failure would have shown as high an incidence of toxic reactions.

With the exception of the relative infrequency of nausea and vomiting, the American literature to date on the digitalis glycoside, digitoxin, has had remarkably little to say about the incidence of other evidences of toxicity.* It is therefore of considerable interest to report these seven cases in some detail.

Case 1. A 46 year old electrical supervisor with rheumatic heart disease, mitral stenosis and insufficiency was admitted to the Peter Bent Brigham Hospital in January 1946 in severe congestive heart failure. Five months before the present admission, he had been treated there because of congestive failure. After receiving 40 cat units of digalen during a 20 day period an attempt was made to lower his apical rate below 80 to 85. To this end he was given digitoxin in the dosage of 0.3, 0.2, 0.4, 0.6, 0.6, 0.8, and 0.2 milligram on seven successive days. At the end of that time digitoxin was stopped because of nausea and vomiting but no unusual tachycardia or ectopic rhythm developed, the apical rhythm remaining in the 80's and the rhythm grossly irregular. He was discharged in good compensation taking 0.2 gram digitalis leaf daily.

Three weeks before his second admission, following a respiratory illness, digitalis was discontinued because of the development of anorexia. A week later digitalis was started again but his symptoms of congestive failure became worse. Five days before admission, he was started on digitoxin, receiving 0.4 milligram daily for two days followed by 0.2 milligram daily for three days. In spite of this his edema increased and his heart rate rose to 120.

Physical examination showed periods of rapid, totally irregular rhythm alternating with bigeminy and bursts of rapid rhythm. Electrocardiograms (figure 1A) showed auricular fibrillation, right axis deviation and premature ventricular beats with bigeminy. In Lead I these were uni-focal but in Lead III they were bi-focal. In Lead CF_2 there was a bidirectional ventricular tachycardia with a rate of 164 beats to the minute, but in the other precordial leads the rhythm was bigeminal. With this evidence of digitalis toxicity digitoxin was discontinued. In a second electrocardiogram taken later that day (figure 1B) three distinct rhythms were

* In a publication appearing since the present paper was written, Master [MASTER, A. M.: Digitoxin intoxication. Jr. Am. Med. Assoc., 1948, cxxxvii, 531] warns that the administration of digitoxin, like that of any other preparation of digitalis, because of the variability in absorption, excretion and therapeutic effect, is an individual experiment.

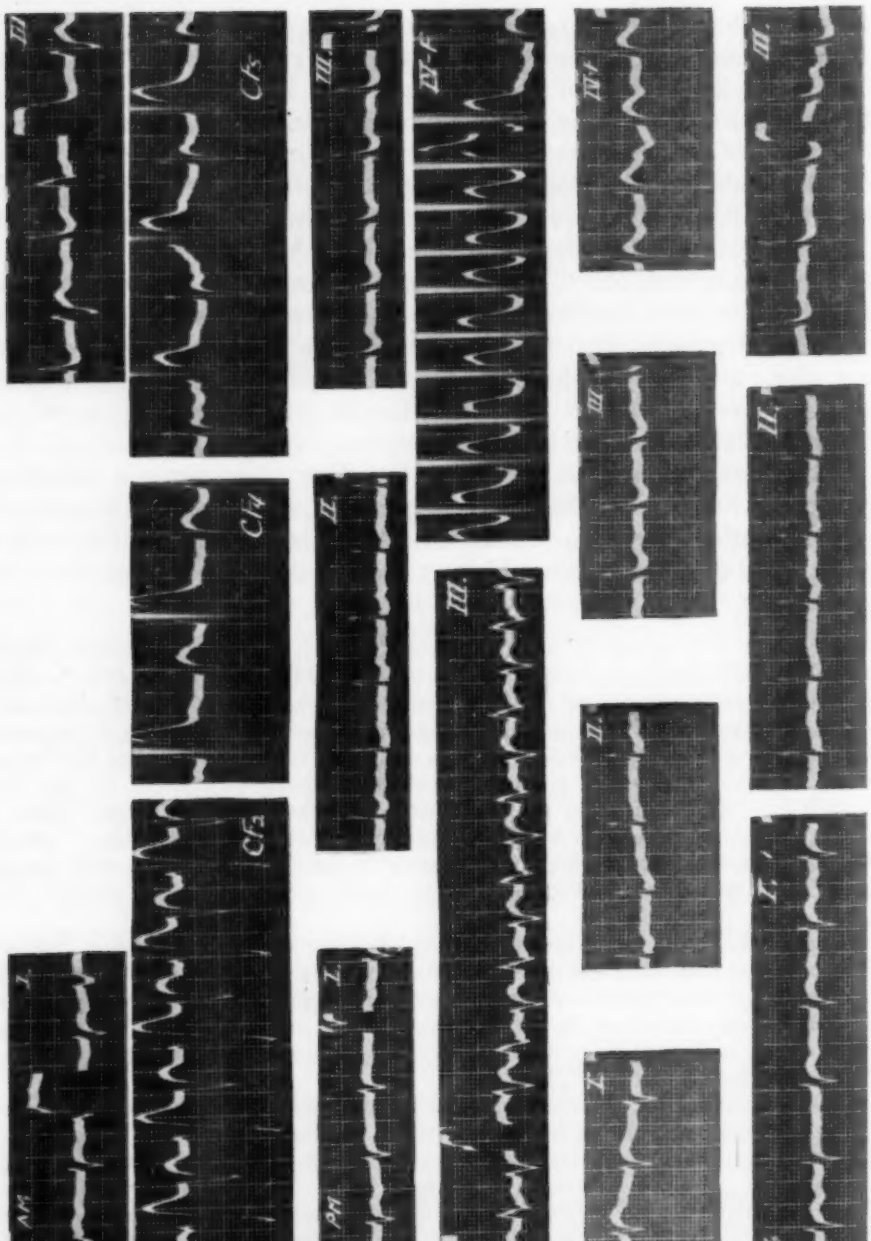

FIG. 1. (Explanation of figure on opposite page.)

recorded. The standard leads showed an idioventricular rhythm with a rate of 104 beats to the minute. Later a bidirectional ventricular tachycardia was seen in Lead III. The rate during this paroxysm was 170 beats to the minute and the rhythm was regular. In Lead IVF a unidirectional paroxysm of ventricular tachycardia was recorded with slight variations in the rate and in the form of the individual ventricular complexes and followed after a compensatory pause by a ventricular complex normal to that lead. The patient was then maintained on quinidine sulfate, 0.2 gram four times daily, for five days.

On the second hospital day (figure 1C) a constant idioventricular rhythm was superimposed on the auricular fibrillation, but there were neither ventricular premature beats nor ventricular tachycardia. The ventricular rate was 108 beats to the minute. On February 2 (figure 1D) auricular fibrillation was recorded as the only arrhythmia with a ventricular rate of 115 beats to the minute.

In spite of these evidences of decreasing toxicity the patient did very badly and died on the ninth hospital day of acute cor pulmonale. Postmortem examination showed infarction of the right lower lobe, right auricular thrombosis and fish-mouth mitral valves.

Case 2. A 59 year old white farmer with hypertensive heart disease and auricular fibrillation, having received digitoxin 0.1 milligram during the preceding six days, was admitted to the Peter Bent Brigham Hospital on October 2, 1946 for the purpose of reverting his heart to normal sinus rhythm and thus to decrease the size of a possibly dilated heart. On admission the rhythm was grossly irregular, the rate 80, but at times the rhythm was regular and at other times coupled. During the first four days he was given digitoxin 0.1 milligram daily without developing gastrointestinal or visual symptoms, but this was discontinued on October 5 when the electrocardiograms showed an abnormal rapid rhythm (figure 2) probably ventricular tachycardia. The heart rate was 152 and the QRS interval 0.13 second. On withholding digitoxin the ventricular tachycardia disappeared to be replaced by the underlying auricular fibrillation. After three days on digitalis leaf, 0.1 gram daily, electrocardiograms showed slowing of the ventricular rate to 72, QRS interval 0.1 second, and there were no premature beats. Accordingly on October 18 he was discharged to the care of his local physician on maintenance doses of digitalis leaf.

Case 3. A 47 year old housewife with rheumatic heart disease, mitral stenosis and insufficiency, developed auricular fibrillation about three weeks before admission. Because of this she was given 1.2 milligram of digitoxin on the third day before admission, 0.8 milligram two days before admission, and 0.2 milligram on the day before admission. Two nights before admission she became nauseated, on the following day she vomited and that evening she developed diarrhea. She noted no visual difficulties.

FIG. 1. (Explanation of figure on opposite page.)

FIG. 1. *Case 1.* Rheumatic heart disease with mild uremia and congestive heart failure. No tendency to tachycardia from 3.1 milligrams digitoxin over seven day period at previous admission. During five days preceding present admission received 1.4 mg. digitoxin without developing gastrointestinal symptoms.

A. Electrocardiograms on admission show auricular fibrillation, right axis deviation, and bigeminal rhythm in Leads I and III and CF_4 and CF_5 with a paroxysm of bidirectional ventricular tachycardia recorded in Lead CF_5.

B. Tracings later that day show: (1) idioventricular rhythm, rate 104 in the conventional leads; (2) bidirectional ventricular tachycardia later in Lead III, the individual ventricular complexes corresponding in form to the premature ventricular beats seen earlier in the day in Lead III (complexes 2 and 4 of the right upper tracing); and (3) classical unidirectional paroxysmal tachycardia in Lead IVF.

C. Second hospital day. Constant idioventricular rhythm superimposed on auricular fibrillation. No ventricular premature beats or ventricular tachycardia.

D. Sixth hospital day. Auricular fibrillation as only arrhythmia. Recovered from digitoxin intoxication on withholding drug but died of pulmonary infarction.

Physical examination on the day of admission, February 3, 1946, showed the heart to be regular and the apical rate to be 140 beats to the minute.

Electrocardiograms (figure 3) showed auricular fibrillation and an idioventricular rhythm, the rhythm being regular and the ventricular rate 140 beats to the minute. The ST segments in Leads II and IVF (the latter not shown in the tracings reproduced) were cupped and depressed and T_3 was inverted.

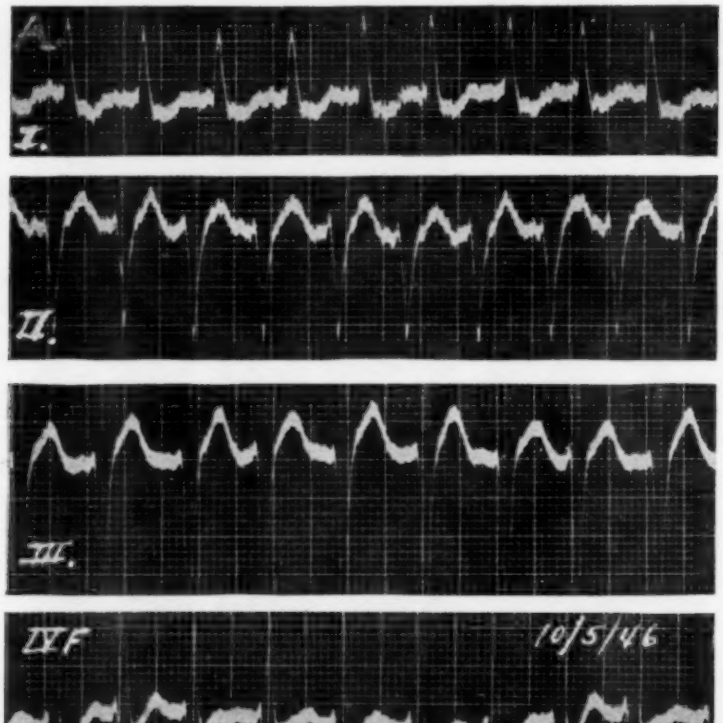

FIG. 2. *Case 2.* Hypertensive heart disease with congestive heart failure. Received 0.1 mg. digitoxin daily for 10 days. No gastrointestinal symptoms.
Third hospital day. Ventricular tachycardia, rate 152, QRS interval 0.13 second. Note very slight irregularity in ventricular rhythm and very slight differences in the appearance of the ventricular complex from cycle to cycle. Ventricular tachycardia disappeared on withholding digitoxin.

Digitalis was withheld until February 3 when the heart had slowed to 90 beats to the minute and had become grossly irregular. On that day she was given 0.3 gram digitalis leaves, on the ninth 0.2 gram, on the tenth 0.3 gram, on the eleventh 0.2 gram, and on the twelfth 0.2 gram. Electrocardiograms at that time showed auricular fibrillation with a ventricular rate of 78. Digitalis leaf was continued 0.3 gram February 13, and 0.1 gram on February 14, 16, and 18, the interval being lengthened because of the re-development of vomiting on February 15. She subsequently reverted to normal rhythm on quinidine therapy. On March 2 she was discharged to the care of her local physician in good condition with no medication. Here then was a patient with a toxic rhythm which subsided on cessation of digitoxin

therapy, following which she was able to take full doses of digitalis leaves with the customary slowing of the ventricular rate.

Case 4. A 77 year old Swedish spinster with hypertensive heart disease, chronic nephritis and auricular fibrillation, was admitted to the Peter Bent Brigham Hospital on February 20, 1946 in cardiac failure and uremia. She had received digitalis leaf 0.2 gram daily for the three days preceding admission.

Examination on admission showed a malnourished elderly lady with an apical heart rate of 108, moderate ankle edema and clear lung bases. Electrocardiograms on admission (figure 5A) showed auricular fibrillation, ventricular rate 98, flat T_1, and left axis deviation.

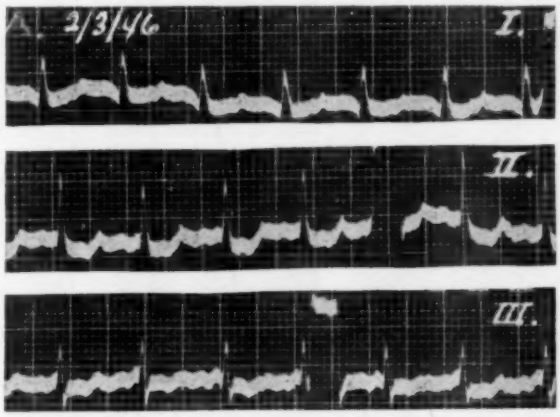

FIG. 3. *Case 3.* Rheumatic heart disease with auricular fibrillation of recent onset. Patient received 2.2 mg. digitoxin over a three day period and developed nausea, vomiting, diarrhea and tachycardia.

Day of admission. Auricular fibrillation and idioventricular rhythm, ventricular rate 140. On withholding digitoxin for five days heart slowed to 90 and became grossly irregular.

Patient subsequently received 1.2 gm. digitalis leaf over five day period. Reverted to sinus rhythm following quinidine therapy disclosing second degree auriculoventricular heart block.

The patient was given digitoxin in the following daily dosage: 0.4 milligram, 0.2 milligram, 0.4 milligram, 0.4 milligram, 0.2 milligram, and 0.2 milligram without developing gastrointestinal or visual symptoms. On the sixth hospital day the pulse rate was found to be 110 and the rhythm regular; the drug was stopped. Electrocardiograms (figure 5B), February 25, 1946, showed auricular fibrillation with idioventricular rhythm, rate 130. Later that evening the same cardiac mechanism was present with heart rate 160 (figure 5C). She died on the following morning. Permission for postmortem examination was not obtained.

It is worthy of comment that from the date of admission to the sixth hospital day the ward officer's notes contained no comment on the heart rate. Yet the nurses' clinical chart (figure 4) showed a radial rate of 112 on the second, 110 on the fourth, and 112 on the fifth hospital day. From the ward officer's notes it seems that this tachycardia was attributed to thyrotoxicosis but the conclusion seems inescapable that if these findings had received the attention they deserved, the drug might have been discontinued at a more opportune time.

Case 5. A 41 year old housewife with rheumatic heart disease, mitral stenosis and insufficiency, auricular fibrillation and mild renal impairment, was first admitted to the Peter Bent Brigham Hospital because of congestive heart failure. On the usual methods of depletion compensation was restored. On the seventh hospital day

she was started on digitoxin 0.1 milligram daily and this was later increased to 0.2 milligram daily. Following discharge she was treated by her local physician with digitoxin 0.2 milligram daily.

Following a week of recurrent congestive failure she was readmitted on August 4, 1946. During the five days preceding this admission she had taken 1.6 milligram

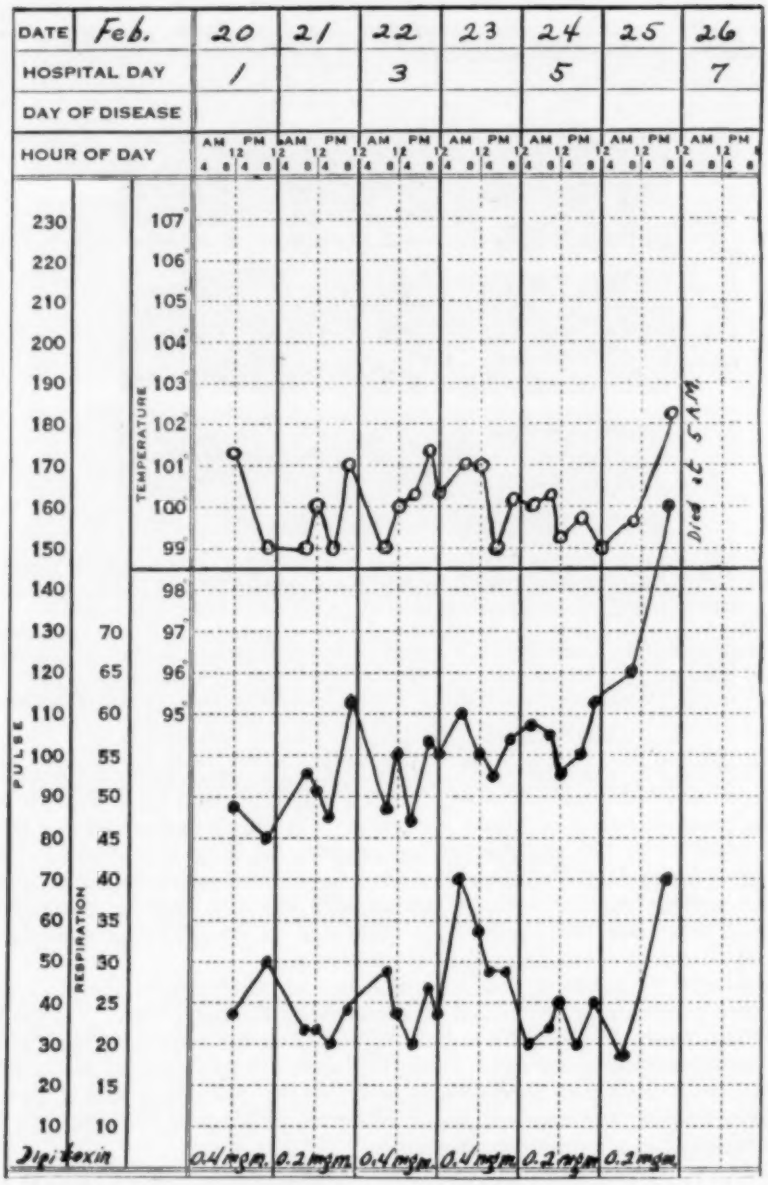

FIG. 4. *Case 4.* Nurse's clinical chart in case of hypertensive heart disease with auricular fibrillation and uremia, showing schedule of digitoxin dosage and recording of tachycardia days before first mentioned by physician on sixth hospital day.

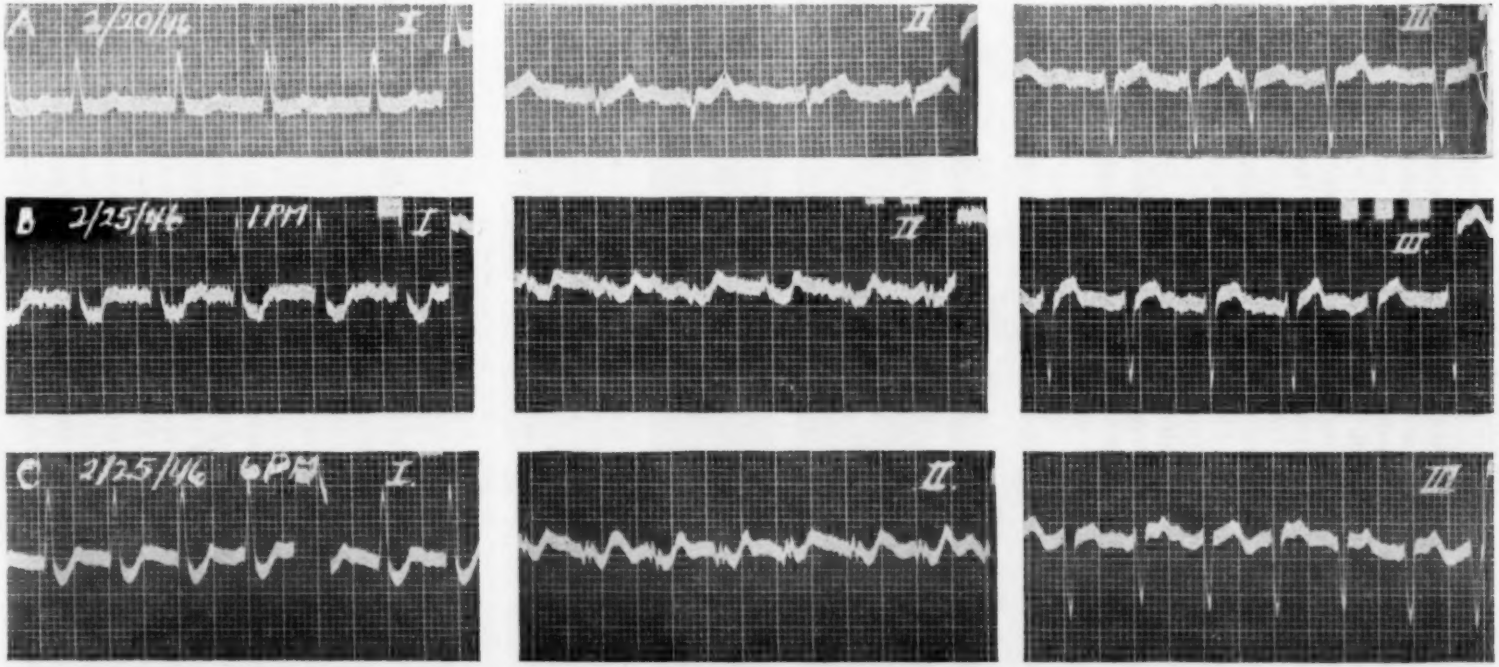

FIG. 5. Case 4. Electrocardiograms from same case.

A. Tracings taken on admission showing auricular fibrillation, ventricular rate 98, flat T_1 and left axis deviation.
B. Sixth hospital day at 1 p.m. Auricular fibrillation with idioventricular rhythm. Ventricular rate 130.
C. That evening at 6 p.m. Same mechanism. Ventricular rate 160. Patient died following morning.

digitoxin but did not develop nausea, vomiting, or diarrhea. On admission the patient was in severe congestive failure with the signs of shock. A leathery friction rub was heard in the right interscapular area. The apical heart rate was 120 beats to the minute and the rhythm coupled.

Electrocardiograms on the second hospital day showed auricular fibrillation, ventricular premature beats, and a ventricular rate of 92. Despite intensive therapy her condition deteriorated rapidly. On the fifth hospital day her pulse had climbed to 130 and she was given 0.2 milligram of digitoxin by mouth, and on the following day 0.4 milligram intravenously. Electrocardiograms August 11, 1946, showed coupled rhythm with a ventricular rate of 114. At 10 a.m. that morning she was given 0.2 milligram of digitoxin. Later that day the heart rate rose to 140. Electrocardiograms (figure 6) showed paroxysmal ventricular tachycardia. Despite 0.5 gram potassium chloride given intravenously the patient died later that day. Permission for postmortem examination was not obtained.

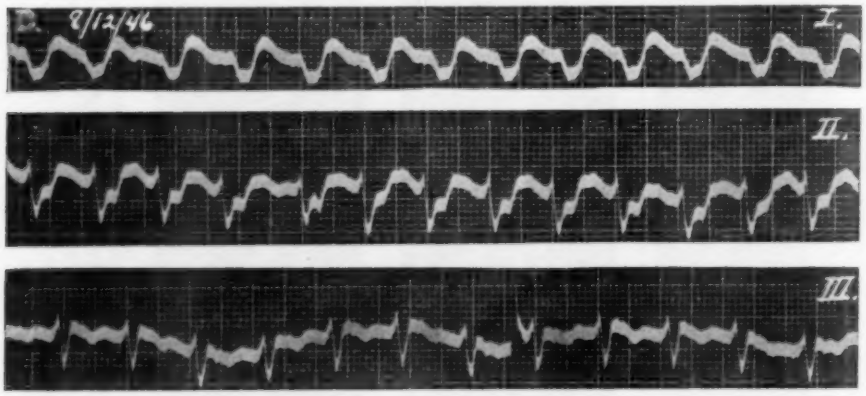

FIG. 6. *Case 5.* Rheumatic heart disease with congestive heart failure, mild pre-renal azotemia and probable pulmonary embolism, apparently already adequately digitalized with digitoxin, then received 1.6 mg. digitoxin during the five days before admission. No gastrointestinal symptoms. On second hospital day electrocardiograms showed auricular fibrillation, ventricular premature beats, right axis deviation with ventricular rate 92. On seventh hospital day bigeminal rhythm was recorded with ventricular rate 114. Another 0.6 mg. digitoxin had been given in desperation in preceding two days. Tracing reproduced was taken on the eighth hospital day. Received additional 0.2 mg. digitoxin as last resort. Terminal ventricular tachycardia.

Case 6. A 79 year old retired French-Canadian carpenter with angina pectoris, an old myocardial infarct and chronic auricular fibrillation was admitted to the Peter Bent Brigham Hospital on April 3, 1947 because of congestive heart failure. For several months he had received digitoxin in doses of 0.2 milligram daily.

Electrocardiograms taken on April 4 showed auricular fibrillation, rate 87 beats to the minute, abnormal form of ventricular complex (T_{1-3} flat) and ventricular premature beats. Accordingly digitoxin, which had been withheld on April 3, was given in dosage of 0.3 milligram on April 4 and 0.1 milligram on April 5. On that date the rhythm as determined at the cardiac apex was, with the exception of a rare ventricular premature beat, quite regular. The patient had not developed gastrointestinal or visual symptoms. Electrocardiograms (figure 7) showed an idioventricular rhythm, rate 108, with rare ventricular premature beats. The ventricular complexes showed QRS intervals measuring 0.18 second in duration and otherwise resembled the typical appearance of left bundle branch block but that diagnosis could not defi-

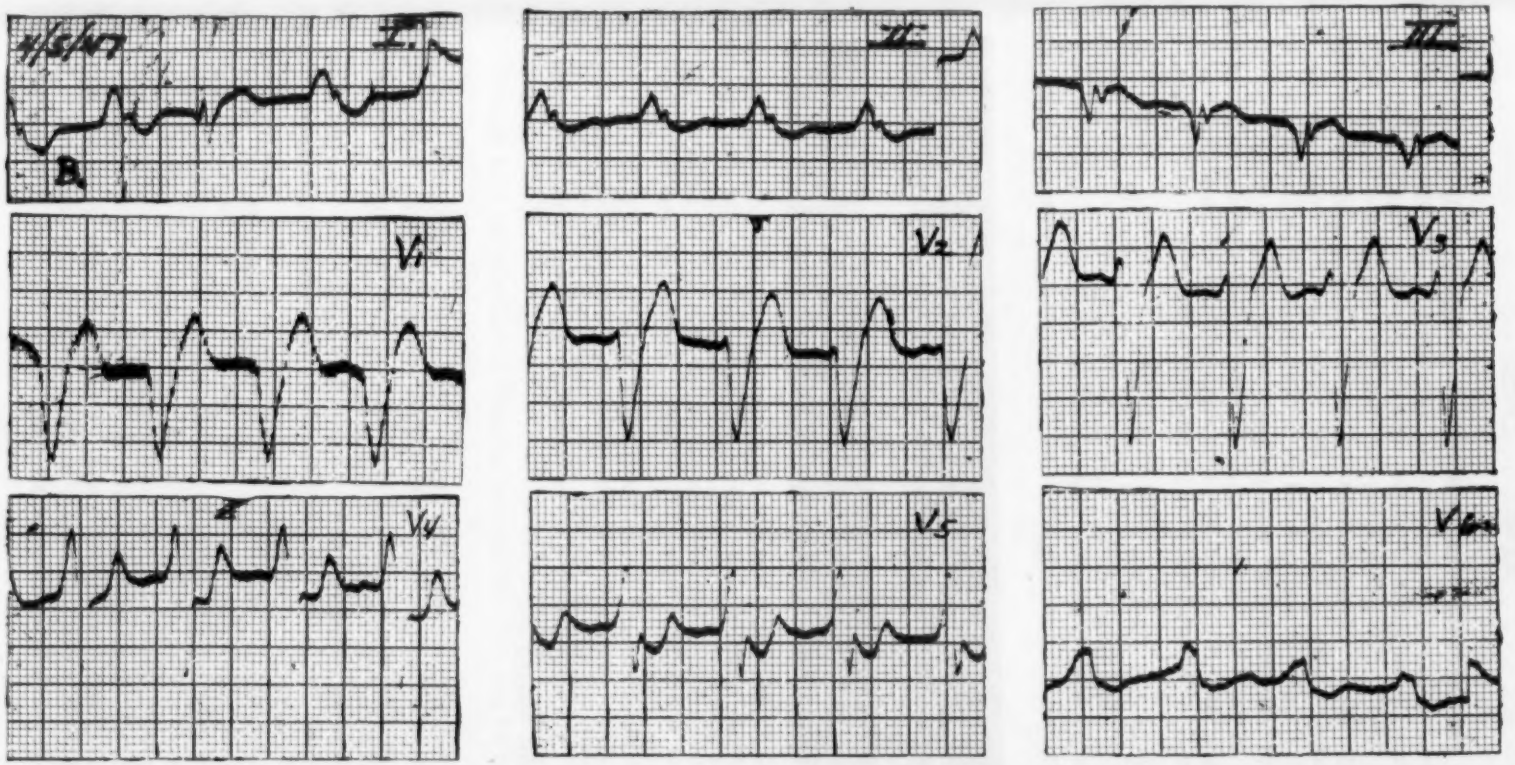

FIG. 7. *Case 6.* Angina pectoris and old myocardial infarct with congestive heart failure. No renal impairment. Maintenance doses of 0.2 mg. digitoxin daily for several months followed by omission of drug for one day. On the second hospital day electrocardiograms showed auricular fibrillation, abnormal form of ventricular complex (T_{1-3} flat) and ventricular premature beats. Ventricular rate 87. Patient given 0.3 mg. digitoxin later that day and 0.1 mg. on the following morning. No gastrointestinal symptoms. Tracing reproduced obtained on third hospital day showing transient idioventricular rhythm with pace-maker below the bifurcation of the common auriculoventricular bundle. Auricular fibrillation. Ventricular rate 108. Digitoxin withheld. Regular rhythm lasted four hours. No recurrence of idioventricular rhythm on subsequent maintenance doses of 0.1 mg. digitoxin daily.

nitely be made because of the presence of auricular fibrillation. Digitoxin was discontinued. This regular rhythm persisted for four hours at a rate of about 100 when the rhythm reverted to auricular fibrillation with the apical rate 72 and the radial rate 52 beats to the minute. Two days later, the idioventricular rhythm having failed to reappear, repeat electrocardiograms were made and showed auricular fibrillation, premature ventricular beats, QRS interval 0.11 second, and ventricular rate 84. On the following day digitoxin was resumed in the dosage of 0.1 milligram every other day, and on April 20 this dosage was increased to 0.1 milligram daily. Following the resumption of digitoxin the patient showed an excellent diuresis, losing 12 kilograms in weight, and subsequent electrocardiograms showed persistent auricular fibrillation without premature beats but with intraventricular block (QRS interval 0.11 second).

Case 7. A 58 year old judge with malignant hypertension, hypertensive heart disease, and myocardial failure in mild uremia, had been receiving digitalis for three years. For two or three months, the patient was not quite certain just how long, he had been taking digitoxin in daily doses of 0.4 milligram. Beginning about three

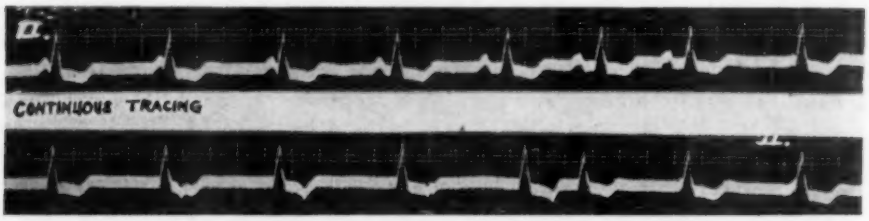

FIG. 8. *Case 7.* Malignant hypertension, hypertensive heart disease, congestive heart failure and pre-renal azotemia. Digitoxin 0.4 milligram daily for two or three months with intermittent gastrointestinal symptoms. Poor response to diuretics.

On second hospital day electrocardiograms showed interference and dissociation with abnormal form of ventricular complex (T_1 inverted, $ST_{1 \text{ and } 2}$ depressed, $T_{2 \text{ and } 3}$ biphasic). Ventricular rate 76. Digitoxin discontinued.

Tracing reproduced obtained on fifth hospital day. Interference and dissociation. Note breaking up of regular rhythm by the fifth, sixth and seventh auricular beats which are conducted and cause ventricles to contract earlier. Retrograde conduction begins at tenth ventricular beat. Third beat from end shows reciprocal rhythm and aberration. Ventricular rate 80. Daily doses of digitoxin 0.1 mg. started two days later. Normal sinus rhythm recorded on twelfth hospital day.

Digitalis leaf 0.1 gm. daily started, well tolerated and followed by good diuresis.

months before admission he had been troubled with weakness, anorexia, nausea, and vomiting but this had cleared only to recur about six weeks before admission. Because of the persistence of these symptoms and a poor response to diuretic medication he was admitted to the Peter Bent Brigham on March 24, 1947.

On admission the cardiac rhythm was grossly irregular and the rate about 100 beats to the minute. Two observers noted marked variations in the intensity of the first sound at the apex.

Electrocardiograms on March 25, 1947 showed interference and dissociation, abnormal form of ventricular complex with inverted T_1, depressed $ST_{1 \text{ and } 2}$ and biphasic $T_{2 \text{ and } 3}$ and were interpreted as characteristic of left ventricular hypertrophy and very suggestive of digitalis toxicity. Digitoxin was discontinued. Tracings taken two days later showed auriculo-ventricular dissociation and sinus arrhythmia. The ventricular rate was 73 beats to the minute. On March 28, 1947 (figure 8) interference and dissociation were again present. The third complex from the end of the strip (Lead II) shows a reëntrant beat with aberrant ventricular conduction. During the next few days the electrocardiogram alternated between periods of interference and

dissociation and apparent normal conduction but eventually settled down to a persistent normal sinus rhythm.

On withholding digitoxin the anorexia, nausea, and vomiting subsided promptly and the patient now responded nicely to diuretic therapy losing seven pounds during his two week hospital stay. He was started on digitoxin 0.1 milligram daily on March 30 and then shifted to digitalis leaf 0.1 gram daily on April 4.

Discussion

The toxic rhythms described are not peculiar to digitoxin. They have been reported [5-26] in patients receiving the leaf of *Digitalis purpurea* and *lanata* and are probably due to one or more of the various bodies contained in the leaf, one of which, indeed, is digitoxin. A review of the general subject of digitalis therapy would be untimely. The interested reader is referred to the recent comprehensive survey of Freedberg and Zoll [27] which deals with digitalis in general and digitoxin in particular.

Five instances of toxicity of the type under discussion among 534 patients receiving digitalis leaf (0.9 per cent) compared with seven instances among 338 patients receiving digitoxin (2.0 per cent) at first sight suggests that the latter preparation is more prone to induce these toxic abnormal rhythms than the former. However, when these figures are subjected to statistical analysis by comparing the standard deviation of the difference (0.86 per cent) with the actual difference (1.1 per cent), that difference is not found to be significant. Hence it cannot be stated as a positive fact that digitoxin has a greater tendency than digitalis leaf to produce toxic reactions. This conclusion holds true whether there are considered to have been five or two toxic reactors among those receiving digitalis leaf.

The clinical impression remains, however, that with digitoxin these rapid rhythms may develop more insidiously than with the leaf. Cases 3 and 7 were the only ones in this series in which nausea, vomiting, or diarrhea was associated with the development of toxic rhythms. In the remaining five the abnormal rhythm itself constituted the first and only evidence of toxicity. The nausea and vomiting caused by digitalis leaf are regarded as due to its local irritant effect upon the gastric mucosa or to a central reflex effect whose mechanism is still disputed. It is held that digitoxin by virtue of the relatively small effective dosage and its virtually complete absorption has very little if any irritant effect upon the gastric mucosa and hence very little tendency to produce nausea and vomiting through a local gastric effect.[1, 2]

The Relation of Dosage to Toxicity

In this group of seven patients developing toxic rhythms, three had received digitoxin in amounts generally considered not to be excessive, while three had received clearly excessive dosage. In the patient (Case 6) who had received maintenance dosage of 0.2 milligram daily for months this amount may have been excessive but this would not explain why the evidences of toxicity had not developed sooner. One patient (Case 1) who

showed toxicity on small doses had received substantially larger doses of the drug at the time of a previous hospitalization without untoward effect. It seems then that toxicity is not synonymous with excessive dosage and that other factors must be involved. This experience is not new. Whereas most of the cases reported by Reid,[9] Luten [10, 11] and Marvin [15] followed excessive doses of digitalis, the majority of investigators [5, 18, 6, 12, 13, 14, 16, 19] were unable to explain the disorders on that basis and attributed them to some cardiac factor such as damaged musculature,[5] a changed state of the heart muscle,[19] an altered state of cardiac nutrition,[12] or to severe heart disease with congestive or anginal failure.[13] Vaughan considered digitalis an "exciting" factor and damaged heart muscle a "predisposing" factor. Although all of Marvin's [15] cases seemed to follow excessive dosage he admitted that other factors than the total amount of the drug, such as congestive heart failure or cardiac enlargement, may be responsible for the onset of these disturbances. Indeed, one might add, it is this very vulnerability of the heart to digitalis in coronary artery disease and coronary thrombosis, that, among other considerations, has militated against its use in those conditions.

It seems unlikely that this problem will be solved until some practical chemical method is available of determining the blood level of digitalis bodies. That this problem may be explained by variation in blood levels secondary to varying renal excretion of the drug is not substantiated by the present experience. The patient in severe uremia (Case 4) happened also to receive excessive doses of digitoxin. Three patients had no evidence of renal impairment and three were in mild azotemia.

More knowledge about the effect of digitalis or digitoxin on the healthy heart might clarify the subject. Our present information is fragmentary and inconclusive. The literature on this point, mostly French, describes, in individuals taking large doses accidentally or with suicidal intent, cardiac slowing from sinus bradycardia, partial auriculo-ventricular heart block, premature ventricular beats,[20, 30, 31, 32, 33] sinus tachycardia (rate 100),[31] or paroxysmal auricular tachycardia [29] but no disturbances of the type described above. However, because the latter are more likely to be associated with a fatal outcome and hence more easily missed, the failure to record them does not rule out their occurrence.

The Family Relationship of the Toxic Tachycardias

In this report the grouping together of these various arrhythmias is deliberate. Idioventricular rhythms, auriculo-ventricular dissociations and ventricular tachycardia can be regarded essentially as different degrees of the same sort of process and varying expressions of the increased irritability of the ventricles. This is well illustrated in Case 1 in which an idioventricular rhythm was recorded on the same day as bidirectional and unidirectional ventricular tachycardia. In this case an identical idioventricular rhythm was again recorded persistently on the following day during the subsidence of

digitoxin effect. It is reasonable to assume conversely that in the development of the more "advanced" toxic rhythms the heart had passed in reverse order through a similar stage of idioventricular rhythm.

The Prevention and Clinical Recognition of Toxicity

Although these abnormal rhythms may be abrupt and unpredictable in their onset they are usually foreshadowed by a rising ventricular rate. It is the duty of the attending physician to detect and evaluate such an increase in heart rate. This may be due to a progression of the underlying disease process or it may be an early indication of imminent digitalis poisoning. In Case 4 the fundamentally serious nature of the patient's illness makes it extremely doubtful that a fatal outcome would thus have been avoided; however, recognition of the rising ventricular rate might conceivably have prevented the development of this patient's terminal tachycardia.

In the absence of a practical chemical test to determine the blood level of digitalis bodies there will almost inevitably be some cases in which the physician is unable to decide whether the rising heart rate is due to a progression of the patient's disease or to digitalis poisoning. After marshaling all available evidence he is compelled to make a gamble one way or the other. The development of abnormal toxic rhythms under such circumstances (e.g. Case 5) can hardly be held to constitute an indictment of digitoxin therapy.

Another clue to the presence of such disturbances is the detection of a sudden change from a totally irregular to a regular rhythm. Although it is possible for the cardiac rhythm to revert from auricular fibrillation to a normal sinus mechanism under digitoxin therapy, it must be remembered that fundamentally digitalis bodies favor the perpetuation rather than the termination of this arrhythmia. All patients showing sudden regularization should therefore be suspected of having developed an idioventricular rhythm with complete auriculo-ventricular heart block or auriculo-ventricular dissociation. This can generally be settled only with the aid of the electrocardiogram.

Digitalis can cause the auricles and ventricles to beat independently of each other by either of two mechanisms. It can so depress auriculo-ventricular conduction that complete heart block is produced with a slower ventricular than auricular rate but generally with a more rapid ventricular rate than occurs in complete block due to most other causes. Or it can so augment the irritability of the ventricles, in the presence of normal auriculo-ventricular conduction, that the ventricles "run ahead" of the auricles. In this case (auriculo-ventricular dissociation) the ventricles beat more rapidly than the auricles. The latter mechanism is illustrated in Case 7, the former in Case 3 in which an underlying complete auriculo-ventricular block was uncovered on reversion of the heart from auricular fibrillation to normal sinus rhythm.

These observations cannot be construed as a deprecation of digitoxin therapy. They serve, rather, to sound a note of greater caution in its use. The freedom from local toxic effects and the more uniform potency of the glycoside have by and large proved a boon to patient and physician alike. But desirable as it is, their absence, in effect, deprives the attending physician of valuable warning symptoms demanding withholding of the drug. It behooves him therefore, in using digitoxin, to be even more on the alert to the insidious development of other evidences of intoxication than with digitalis leaf.

Summary

The percentile incidence of toxic rapid rhythms was greater in a group of general hospital patients receiving digitoxin than in those receiving digitalis leaf, but the difference was not statistically significant. Seven cases of digitalis poisoning among 338 patients receiving digitoxin comprised three instances of paroxysmal ventricular tachycardia, three of idio-ventricular rhythm, and one of interference and dissociation. In three cases the dosage of digitoxin was, and in three it was not, excessive. In the seventh it may have been excessive. Due to the freedom from local toxic effects with digitoxin, these toxic rhythms may be more insidious in their onset than with digitalis leaf. A rising ventricular rate or the sudden regularization of a totally irregular rhythm may serve as clues to the imminence in the one case, or the inception in the other, of these abnormal disturbances of rhythm.

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THE HEART IN THE TERMINAL STATE: EFFECT OF INTRACARDIAC EPINEPHRINE *

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As a consequence of recent animal experiments demonstrating the possibilities of revival of organisms, much interest has been aroused regarding the mode of death of the human heart particularly in regard to its functional deterioration. In addition, a study of the dramatic effect of intracardiac therapy on the terminal heart in patients dying from various diseases has been considered by us as a field of paramount importance particularly since we have had occasion to witness recently several instances of precipitous, unexpected, and unexplained death.

Objective studies of the effect of death on the heart must depend in great part on the use of electrocardiography, which in addition to increasing profoundly our knowledge of the heart in health and disease has aided greatly in the investigation of the heart in its clinical and subsequent biologic death. The electrocardiogram has demonstrated repeatedly that clinical death characterized by the disappearance of heart sounds and cessation of respiration is followed in many cases for a variable and at times a prolonged period by cardiac activity. Certain measures designed to revive a dying myocardium may some day make possible resumption of circulation adequate for continuation of life for a time. This possibility makes desirable an analysis of any knowledge which exists at present or which may be obtained in this investigation, concerning the sequence of events immediately preceding the total cessation of cardiac activity.

Review of Literature

The original work of Rohmer [1] in 1911 represents the first reference to electrocardiograms taken during the last moments of human life. Rohmer pointed out that in three fatal cases of diphtheria, terminally the auricles and ventricles beat independently and that the QRS complex assumed an abnormal form. Robinson [2] in 1912 published a study of electrocardiographic observations made in seven patients dying of acute infectious diseases. In four cases ventricular activity outlasted the auricular activity while in two the reverse was true. Cardiac activity was revealed by the electrocardiograph, six to 35 minutes after all the usual clinical signs of death had appeared. Marked slowing of the rate of cardiac activity always occurred and there was usually distinct delay in the conduction time between auricles and ventricles. Ventricular fibrillation occurred in only two cases and in one

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of these, a sinus rhythm was transiently reëstablished. Eventual fusion of the R- and T-waves was a constant occurrence. Auricular fibrillation was not encountered.

In 1915 Halsey [3] described an almost complete electrocardiographic record of the heart during the last moments of a patient dying from bronchopneumonia. Slowing of the heart rate was marked, then increasing auriculoventricular conduction occurred with appearance of abnormal QRS complexes and ventricular fibrillation appeared shortly before death. Dieuaide and Davidson [4] in 1921 reported records of patients dying of intrinsic heart disease in two of which the electrocardiograms were taken during death resulting from arteriosclerotic and hypertensive heart disease. Slowing of the cardiac rate occurred along with lengthening of the P–R and QRS intervals, appearance of auriculoventricular nodal rhythm, complete dissociation of auricles and ventricles and various arrhythmias including auricular and ventricular extrasystoles, ventricular tachycardia and auricular and ventricular fibrillation. Schellong [5] in 1923 found similar phenomena to occur in electrocardiograms based on studies in 20 dying patients. In addition he pointed out that T-waves in dying hearts were noted to increase in size and become positive even when previously negative. Willius [6] in 1924 presented a study on changes in the mechanism of the human heart preceding and during death. He found that in each instance of six patients, auricular activity ceased before that of the ventricles. Nodal rhythm occurred frequently as did complete heart block. Ventricular fibrillation appeared in four cases and was the terminal mechanism in three. Periods of cardiac standstill occurred lasting from 9.4 to 11.4 seconds. He concluded that the terminal changes in the mechanism of the human heart probably resulted from vagal influences and from alterations in the inherent activity of the heart due to the influences accompanying death.

An interesting study on the dying human heart by Kahn and Goldstein [7] in 1924 stressed the initial failure of the sinus node with the assumption of control by the auriculo-ventricular node as the most significant phenomenon in terminal heart activity. They pointed out that the sinus node first shows irritability and depression in various sequences and in varying degree and if such disturbances could be controlled before cessation of sinus function, recovery might occur. Martini and Sckell [8] in 1928 studied 17 patients and found similar terminal phenomena to those which had been previously published. Fatigue of the sinoauricular node resulted in an auriculoventricular nodal rhythm. The R- and T-waves tended to merge. The longest interval in which electrical manifestations persisted after clinical death was nine and a half minutes. Turner [9] in 1931 reviewed electrocardiographic observations on the death of the human heart in 65 cases contained in the literature and presented a detailed study of five cases of his own. He found as did the others that conspicuous slowing of the heart rate was the most constant change in the cardiac mechanism immediately preceding death. Also frequently encountered was the appearance of an auriculoventricular nodal

rhythm or an idioventricular rhythm. The age of the patient or the presence or absence of cardiac disease did not condition the manner in which the heart died. Significant changes appeared in the electrocardiogram often only a few minutes before clinical death. Hanson, Purks, and Anderson [10] a few years later (1933) reported 25 cases in which electrocardiograms were taken during death. They encountered 10 instances of ventricular fibrillation and this rhythm represented the terminal event in cessation of cardiac activity in nine of the 25 cases. The sequence of events otherwise was similar to those of previous reports. The last five cases of their series after standstill of both the auricles and ventricles had occurred, were treated with intracardiac injection of adrenalin in the third left intercostal space close to the sternum and in four of them a transient return of monophasic complexes appeared in the electrocardiogram only to end in terminal ventricular fibrillation.

Sigler and co-workers [11] in 1937 reported electrocardiographic studies on 20 cases before, during, and after clinical death. In some instances electrocardiographic activity was noted as long as one hour after clinical death. The main changes noted included initial sinus acceleration followed by sinus bradycardia, sinoauricular standstill and then nodal rhythm, ventricular extrasystoles, increasing and variable auriculoventricular block, intraventricular block, changes in ventricular complexes, variable cessation of auricular activity and ventricular fibrillation. Levin [12] in 1939 published a good description of two terminal electrocardiograms and concluded that death of the heart occurred in three phases, first sinus bradycardia due to apnea, then either a nodal or ventricular rhythm and finally a slow rhythm with huge T-waves and gradual cessation. In the foreign literature Mayer, Pataro and Lepera [13] in 1941 reviewed the literature and discussed a patient in whom an injection of intracardiac adrenalin was given at clinical death and resulted in transient changes from nodal rhythm to sinus rhythm for the 33 minutes in which the electrocardiogram was followed.

Resuscitation of the Heart

Hyman [14] in 1930 published an excellent report on the resuscitation of the stopped heart by intracardiac therapy. He pointed out that the increasing use of epinephrine for intracardiac injection in emergency conditions arising in the operating room as well as elsewhere has been attended by such inconstant results that physicians are at a loss in evaluating the efficacy of the procedure. As a result he attempted a systematic study of this problem. In a review of the literature he found that the intracardiac method of resuscitation had been employed in a total of about 250 cases up to 1930 and that a favorable outcome appeared to be experienced in about 25 per cent. Levine and Matton [15] in 1926 reported a case of Adams-Stokes syndrome wherein ventricular fibrillation occurred for a period of 3.5 minutes and was followed by ventricular standstill for 79 seconds in which intracardiac injection of

adrenalin returned the mechanism to a normal rhythm enabling the patient to leave the hospital.

Intracardiac injection has been considered as including either injection into the wall of the heart or the chambers of the heart particularly that of the ventricles. Any other intravenous route of medication would obviously be ineffective since in such instances circulation is at a standstill. Further consideration also led Hyman to believe that injection into the chambers of the heart would be just as ineffective since with cardiac cessation there is no more circulation within the cardiac chambers than in the arterial or venous circulation. He recommended injection of the drug in the wall of the heart based on experience in the experimental laboratory in which the isolated mammalian heart may be stimulated to contraction following a period of standstill when epinephrine and other substances are injected into the myocardium. Occasional favorable results have also resulted clinically from the use by the intracardiac injection of such drugs as digitalis, camphor, ether, strophanthin, metrazol, coramin, strychnine, hypertonic salt solution, caffeine and dextrose. The large number of substances used for intracardiac therapy suggests that the effect of these drugs may be somewhat non-specific in their action.

Resuscitation of the heart by direct or indirect manipulation has been practiced for many years by numerous surgeons for cardiac arrest during surgical procedures. The attempt is made to massage the heart by direct pressure on the diaphragm or thorax or by squeezing, pinching or any mechanical means of irritating the heart to contract again. Various mechanical devices for stimulating the heart have been devised. However, in a patient dying from a non-surgical condition there is no opportunity mechanically to stimulate the heart. Obviously a direct and rapid route of cardiac stimulation is indicated in dying patients. Hyman concluded that the intracardiac injection procedure is satisfactory and its effectiveness is due primarily to the effect of the puncture wound on the myocardium rather than to the chemical substance injected. Anoxemia makes the myocardium irritable and any mechanical stimulation such as massage or injecting a needle may produce a wound which becomes a focus of increased irritability from which a stimulus may develop and produce initially extrasystoles and subsequent sinus rhythm and recovery, although with more prolonged anoxemia and permanent ventricular muscle changes abnormal rhythm such as ventricular fibrillation may result with no opportunity of resuscitation. For this latter reason Hyman recommended intracardiac puncture be made into the right auricle and stressed that the auricles are more responsive to mechanical stimulation than the ventricles.

For clinical purposes, the patients favorable for resuscitation are those in whom the heart is relatively normal and where there is no serious generalized disease. Especially favorable situations are those instances of cardiac arrest on the operating table, during anesthesia, shock, accidents, sudden collapse, so-called "status lymphaticus," and asphyxia neonatorum. An-

other important consideration is the period which has elapsed between the time of arrest of the circulation and the attempt at resuscitation. Particular study has been made of the exact duration of time during which the circulation can be arrested before nerve cells die and vital centers cannot be revived. However, there has been no uniformity of opinion in this regard. In human beings, clinical and pathologic studies are lacking on the effects of anoxia and the resultant neuronal damage due to cardiac arrest. Although successful cardiac massage has been performed by numerous surgeons for cardiac arrest during surgical procedures, permanent success without cerebral damage has been limited to cases in which the critical time limit of five minutes has not been exceeded. Three British investigators [16] have recently reported a case of prolonged cardiac arrest occurring during surgical intervention. The fatal duration of cardiac arrest was 10 to 11 minutes. Transdiaphragmatic cardiac massage was successful in reëstablishing the cardiac beat. During the survival period of 26 days the patient's condition resembled modified decerebrate rigidity and she died of intercurrent infection. Obviously therefore attempts at resuscitation must be performed not only skillfully but also speedily before the extreme sensitivity of the brain to anoxemia, ischemia, and anemia has resulted in irreparable and irreversible damage.

Method of Study

This paper presents electrocardiographic changes occurring before, at the time of, and after clinical death in a series of 34 cases. In many instances tracings were started several hours before expected death and continued from time to time until biologic death occurred. In addition many of the patients had electrocardiograms for days, weeks, or even months prior to the fatality. In our series an attempt was made to obtain tracings in the standard and CF4 leads during the early events preceding death but shortly before and after death events were recorded only in Lead II. In most instances, complete data were obtained including the chronologic occurrences in reference to the electrocardiograms of clinical death, cessation of heart sounds and respiration, and the time of appearance of the very last complex in the heart tracings. Factors such as age, sex, primary and immediate cause of death, cardiac status, clinical findings, such as terminal temperature, blood pressure, presence of shock or cardiac failure, presence or absence of anemia, and findings at autopsy were all studied and attempts made at correlation with the terminal findings in mind.

In addition to the study on the nature and mode of cessation of cardiac activity, equal consideration was given to the effect of intracardiac injection of 1 to 2 c.c. of 1–10,000 solution of epinephrine both directly into the myocardium and into the cardiac chambers usually immediately after all the deflections in the electrocardiogram had ceased. This part of the study presented an opportunity to study the physiologic ramifications of the intra-

cardiac injection method of resuscitating the dying heart. The intracardiac injection was performed by using a 21 gauge 4 inch length needle and inserting it slowly into the fourth left intercostal space and pulling on the plunger of the syringe until blood was obtained and then injecting the epinephrine. The myocardial infiltration was performed in essentially the same manner except that when the point was reached at which the blood was obtained, the needle was withdrawn extremely slowly until the exact point was reached when blood could just no longer be obtained and then the epinephrine was injected presumably into the myocardium.

Results

This series included 23 males and 11 females. The causes of death varied and included among other conditions, 11 patients with some form of heart disease and 11 with carcinomatosis. The duration of the primary disease varied from four weeks to 12 years. The ages varied from 18 to 79 years with an average of 57.4 years. Twenty-four of the 34 patients had postmortem examinations. Terminally most of the patients were mentally in a comatose or markedly obtunded condition. With the exception of one patient who had an exploratory thoracotomy, none of the deaths were postoperative. Various medications were given in the terminal period but these appeared to have no specific influence on the course of the patients in the final stages. Terminal temperatures varied from subnormal to very high ranges. Seven of the 34 patients had for comparison one or more electrocardiograms previous to their terminal illness. The terminal electrocardiograms were begun over a range of 1 to 35 minutes (average of 9.2 minutes) before cessation of respiration, and continued for a period of 50 seconds to 22 minutes (average of 5.9 minutes) after respiration had ceased. In 11 of the 34 patients in whom sufficient attention could be spared it was noted that the terminal complex in the electrocardiogram occurred 3.3 to 17 minutes (average of 5 minutes) after the heart beat became imperceptible.

Summary of Electrocardiographic Changes

Table 1 contains a summary of the terminal electrocardiographic changes. In the records taken early in the terminal period 30 cases presented a sinus rhythm and four auricular fibrillation. One case had left bundle branch block. A great variety of rapidly shifting arrhythmias and changes in rate occurred. Initial sinus acceleration of the cardiac mechanism was frequent, but slowing of the rate prior to death was always encountered with the exception of two patients in whom an abrupt change of the mechanism to ventricular tachycardia occurred. With progressive sinus slowing and associated sinoauricular node depression, periods of sinoauricular block appeared in three cases. Sinoauricular standstill occurred in five patients. During life, when sinus node depression and inhibition occur, the center of next greatest inherent rhythmicity, which is usually the auriculoventricular

TABLE I

Summary of Terminal Electrocardiographic Changes

Case No.	Age	Sex	Diagnosis	Sequence of Events in Electrocardiogram
1	62	M	Portal cirrhosis; bleeding esophageal varices	Progressive prolongation of P–R interval; 3 to 1 A–V block; cessation of ventricles; cessation of auricles.
2	55	M	Hypertensive heart disease; acute posterior myocardial infarction	Changes of acute posterior myocardial infarction; ventricular extrasystoles; complete A–V block; ventricular extrasystoles from 3 foci.
3	53	F	Portal cirrhosis	Abnormal form of ventricular complex with low voltage, sinus tachycardia, auricular extrasystoles; sinoauricular block; nodal rhythm, 45 per minute; complete A–V block, 25 per minute; markedly abnormal ventricular complex; cessation of ventricle; cessation of auricle; epinephrine given, no effect.
4	52	M	Congenital heart disease; tetralogy of Fallot	S-type bundle branch block; nodal tachycardia; cessation of auricles; idioventricular rhythm, rate 48 per minute; ventricular extrasystoles.
5	72	F	Acute posterior myocardial infarction; bronchopneumonia	Changes of acute posterior myocardial infarction, auricular fibrillation, left axis deviation; auricular fibrillation, with complete block; idioventricular rhythm 38 per minute; asystole for 10 seconds; sinus rhythm.
6	79	F	Acute myocardial infarction; arteriosclerotic heart disease; auricular fibrillation	Myocardial damage of coronary type, auricular fibrillation, ventricular extrasystoles, digitalis effect; gradual slowing of ventricular beats to 25 per minute, then 12 per minute and then complete cessation.
7	18	F	Rheumatic heart disease with aortic stenosis and insufficiency and mitral stenosis and insufficiency	Auricular fibrillation with ventricular extrasystoles; auricular flutter with 5 to 1 block, cessation of ventricle; regular auricular beats with progressive slowing.
8	55	M	Squamous cell carcinoma of larynx; bronchopneumonia	Sinus rhythm; sinus bradycardia; nodal tachycardia; ventricular tachycardia; ventricular flutter, ventricular fibrillation.
9	56	M	Carcinoma of stomach with metastases	Sinus rhythm; sinus bradycardia; runs of nodal extrasystoles; nodal rhythm, markedly abnormal ventricular complexes with QRS duration of .24, depressed ST complexes and low voltage.
10	69	M	Carcinomatosis; bronchopneumonia	Abnormal form of ventricular complex, low voltage; sinus tachycardia; sinus bradycardia; prolonged P–R interval; partial heart block; cessation of ventricle; cessation of auricle; epinephrine given, no effect.
11	40	F	Myelogenous leukemia	Abnormal form of ventricular complex, low voltage, sinus bradycardia, sinoauricular block; ventricular extrasystoles.
12	68	M	Arteriosclerotic heart disease	Myocardial damage of coronary type; sinus tachycardia; sinus bradycardia; partial heart block, nodal rhythm, idioventricular rhythm.

TABLE I—*Continued*

Case No.	Age	Sex	Diagnosis	Sequence of Events in Electrocardiogram
13	65	M	Arteriosclerotic heart disease; acute posterior infarction	Changes of an acute posterior myocardial infarction; sinus tachycardia; sinus bradycardia; ventricular extrasystoles from 2 foci; asystole for 53 seconds; ventricular fibrillation; idioventricular rhythm with progressive slowing.
14	67	M	Arteriosclerosis; diverticulosis of colon; acute anterior myocardial infarction	Changes of an acute anterior myocardial infarction; sinus bradycardia; complete A–V block; auricular standstill; markedly abnormal ventricular complex with extreme slurring, duration of .24, elevation of ST segments; epinephrine given, no effect.
15	67	M	Arteriosclerotic heart disease; prostatectomy 4 days before death	Abnormal form of ventricular complex, sinus rhythm; ventricular tachycardia; asystole for 33 seconds; cessation of auricle; idioventricular rhythm at 30 per minute with progressive slowing.
16	38	F	Myelogenous leukemia	S-type bundle branch block, sinus rhythm; prolonged P–R interval; partial heart block; varying periods of auricular standstill; complete heart block.
17	58	M	Bronchiogenic carcinoma; exploratory thoracotomy	Abnormal form of ventricular complex; sinus tachycardia; sinus bradycardia; nodal rhythm; complete A–V block; auricular standstill; idioventricular rhythm becoming irregular; very abnormal ventricular complexes with depressed ST complexes and QRS duration of .30; epinephrine given with production of a short run of regular ventricular beats.
18	28	M	Carcinoma of lung	Sinus rhythm, sinus tachycardia; sinus bradycardia, partial heart block changing from 2 to 1 to 4 to 1; cessation of ventricle, cessation of auricle, epinephrine given, no effect.
19	66	M	Carcinoma of trachea	Myocardial damage of coronary type; sinus rhythm; auricular standstill; alternating bundle branch block; ventricular extrasystoles.
20	57	M	Reticulum cell sarcoma; bronchopneumonia	Sinus rhythm; nodal rhythm with progressive slowing; epinephrine given; mixed ventricular flutter and fibrillation for 2 minutes.
21	66	F	Carcinoma of gallbladder	Abnormal form of ventricular complex, sinus rhythm; shifting auricular pacemaker; nodal beats; ventricular extrasystoles.
22	54	F	Leukosarcoma; lobar pneumonia	Sinus rhythm; sinus bradycardia; 2 to 1 A–V block; auricular standstill; epinephrine given; ventricular rate increased; auricular beats reappeared, sinus bradycardia; sinus pauses; irregular nodal beats.
23	49	M	Adenocarcinoma of liver	Abnormal form of ventricular complex; auricular fibrillation; ventricular fibrillation; epinephrine given, no effect.
24	75	M	Adenocarcinoma of ? origin	Sinus rhythm; nodal rhythm; idioventricular rhythm; markedly abnormal QRS complexes with duration of .32, depression of ST segments; epinephrine given; change to sinus rhythm with normal ventricular complexes; contractions continued for 36 minutes after cessation of respiration.

TABLE I—*Continued*

Case No.	Age	Sex	Diagnosis	Sequence of Events in Electrocardiogram
25	53	M	Myelogenous leukemia	Sinus rhythm; sinus bradycardia; nodal rhythm; ventricular extrasystoles; ventricular tachycardia; ventricular fibrillation; epinephrine given, no effect.
26	72	M	Severe anemia; shock	S-Type bundle branch block; low voltage; ventricular extrasystoles, cardiac standstill; epinephrine given in ventricular chamber, no effect; given in myocardium, ventricular beats obtained for 1.5 minutes; myocardial injection repeated, no effect.
27	59	F	Carcinoma of ovary with metastases to lung	Myocardial damage of coronary type; sinus rhythm; sinus bradycardia; partial heart block; idioventricular rhythm; mixed ventricular flutter and fibrillation; epinephrine in cardiac chamber; no effect; myocardial injection given, ventricular fibrillation.
28	62	F	Generalized carcinomatosis; bronchopneumonia	Myocardial damage of coronary type; sinus tachycardia; sinus bradycardia, sinoauricular block; nodal rhythm; cessation of ventricle, cessation of auricle; epinephrine given in myocardium, no effect.
29	78	M	Chronic lymphatic leukemia	Left bundle branch block, sinus rhythm; shifting auricular pacemaker; auricular extrasystoles, nodal extrasystoles; epinephrine given in cardiac chamber, no effect.
30	52	M	Adenocarcinoma of liver	Abnormal form of ventricular complex, sinus rhythm, sinus tachycardia; sinus bradycardia to 15 per minute; epinephrine given, no effect.
31	51	M	Subacute glomerulonephritis	Sinus rhythm, sinus bradycardia; nodal rhythm, complete A–V block; irregular ventricular beats, cessation of ventricle; cessation of auricle; epinephrine given, no effect.
32	61	M	Hypertensive heart disease	Abnormal form of ventricular complex; sinus rhythm, ventricular fibrillation.
33	39	F	Malignant hypertension	Abnormal form of ventricular complex, sinus rhythm; sinus bradycardia, ventricular tachycardia, asystole for 11 seconds; ventricular fibrillation; epinephrine given into right auricle, no effect.
34	56	M	Hypertension; uremia	Auricular fibrillation; complete A–V block; epinephrine given in myocardium; ventricular fibrillation; asystole for 1 minute; mixed ventricular flutter and fibrillation; ventricular fibrillation.

node, becomes the pacemaker. A similar mechanism developed in these terminal records for auriculoventricular nodal rhythm appeared in 11 and an idioventricular rhythm in seven more of the 34 cases. Ventricular extrasystoles assumed control at intervals in nine patients with multiple foci in two instances, while nodal and auricular extrasystoles appeared in five cases.

As death became very imminent, increasing auriculoventricular conduction was a fairly common finding with the development of partial heart block in five instances and complete block in eight cases. Most of the usual arrhythmias were encountered in these terminal records. Auricular fibrilla-

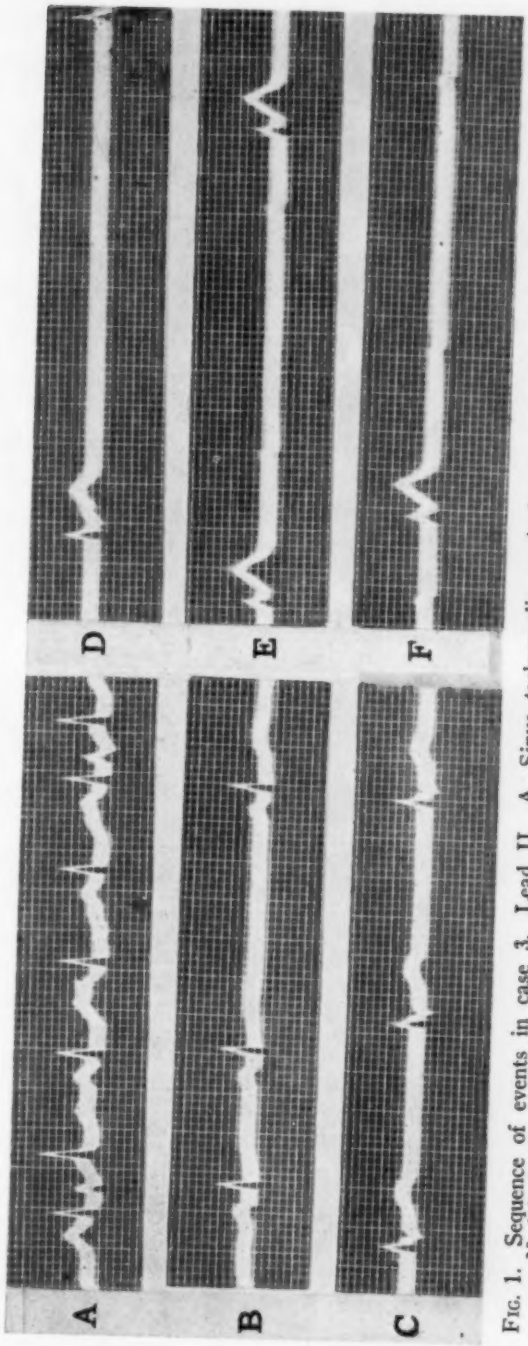

FIG. 1. Sequence of events in case 3. Lead II. A. Sinus tachycardia, auricular extrasystoles. B. Sino-auricular block. C. Nodal rhythm. D. Complete A–V block. E. Abnormal ventricular complexes. F. Initial cessation of ventricle.

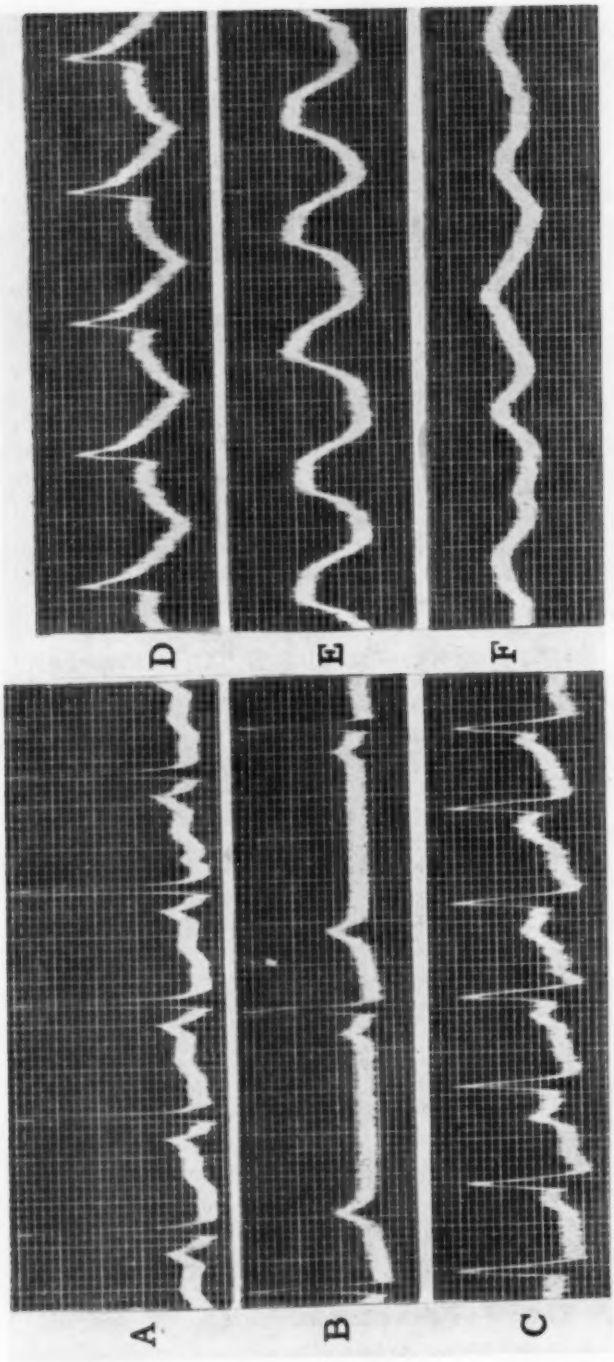

FIG. 2. Sequence of events in case 8. Lead II. A. Sinus rhythm. B. Sinus bradycardia. C. Nodal tachycardia. D. Ventricular tachycardia. E. Ventricular flutter. F. Ventricular fibrillation.

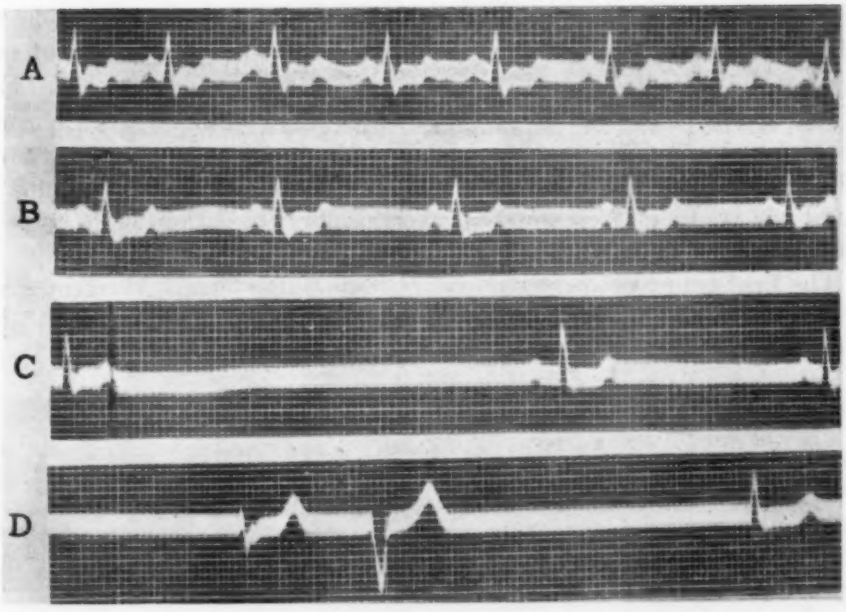

FIG. 3. Sequence of events in case 11. Lead II. A and B. Sinus rhythm. C. Sinoauricular block. D. Ventricular extrasystoles.

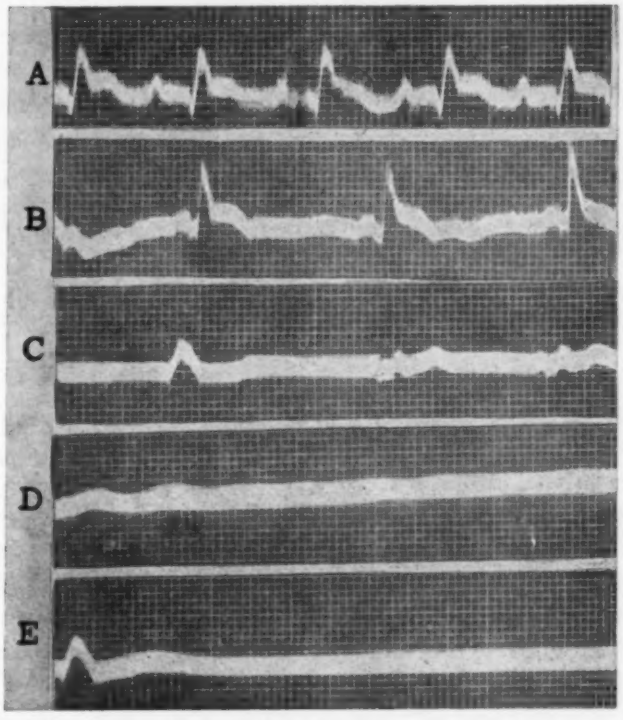

FIG. 4. Sequence of events in case 13. Lead II. A and B. Changes of acute posterior infarction with sinus rhythm. C. Ventricular extrasystoles from two foci. D. Asystole lasting 53 seconds. E. Idioventricular rhythm with progressive slowing.

tion, however, did not occur with the exception of the four patients who had had this rhythm prior to the onset of the terminal state; in one of these instances the auricular fibrillation changed to auricular flutter. Ventricular fibrillation was fairly common having been encountered in nine cases, usually as a terminal event, whereas ventricular tachycardia and ventricular flutter each occurred in four patients. The latter two ventricular rhythms appeared always in association with ventricular fibrillation with only one exception.

The final complex in the electrocardiogram after death represented ventricular activity in 27 instances and auricular activity in seven cases. Intra-

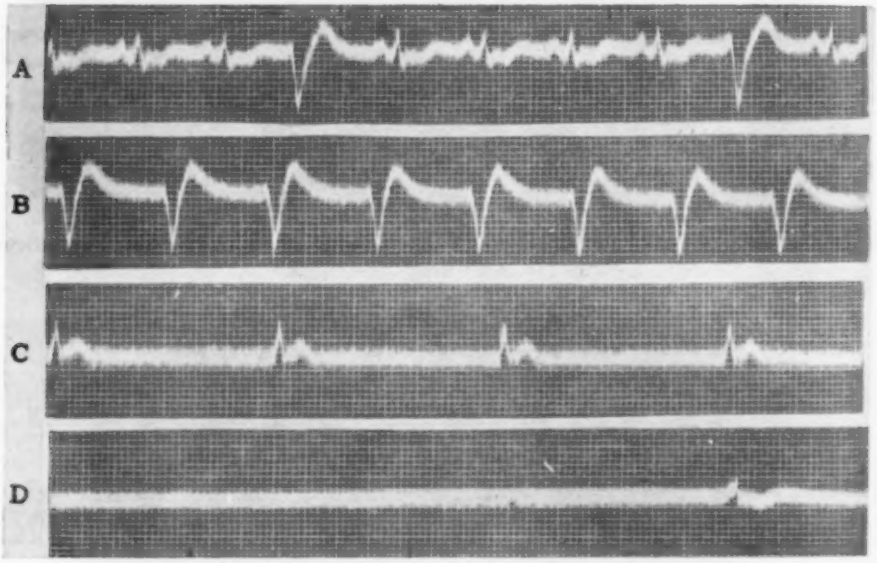

FIG. 5. Sequence of events in case 15. Lead II. A. Sinus rhythm with ventricular extrasystoles. B. Ventricular tachycardia. C and D. Idioventricular rhythm with progressive slowing.

ventricular disturbances included particularly marked prolongation of the QRS duration (maximum of .52 second) in 28 patients with associated slurring especially of the S-wave. The voltage of the QRS complex was low in 20 cases and increased in only one. Various changes occurred in the character of the RST segments including elevation, depression, rounding and lengthening. The T-waves often changed precipitously by becoming inverted, upright, abnormally high or isoelectric. Significant periods of asystole of both the auricle and ventricle occurred in six cases with the asystolic period varying from 10 to 60 seconds. Figures 1 to 11 illustrate the sequence of events and terminal occurrences in characteristic cases.

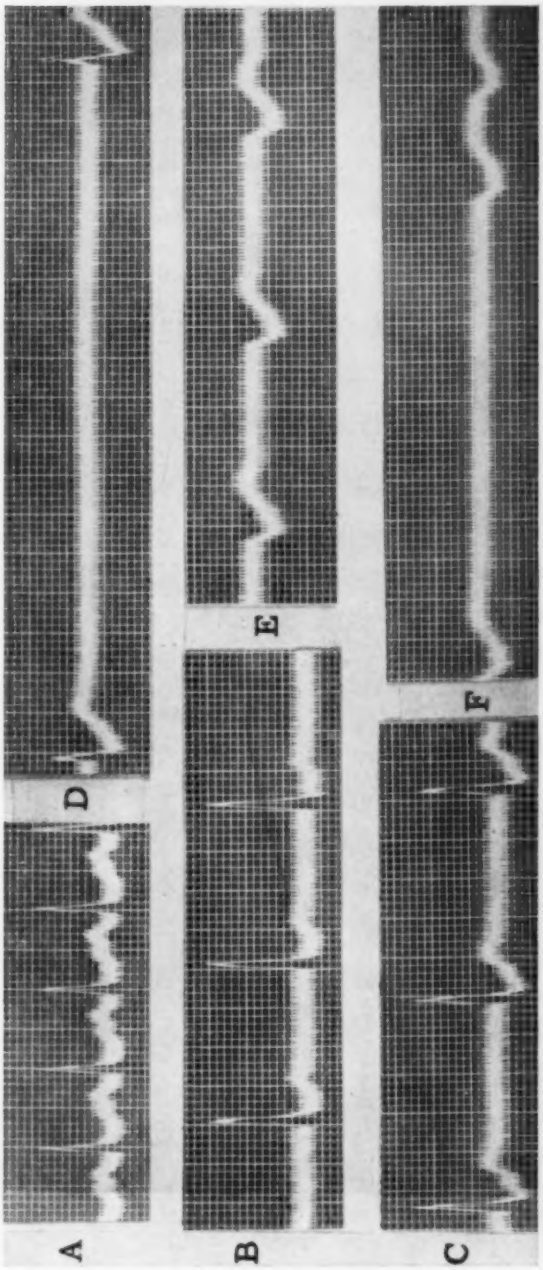

FIG. 6. Sequence of events in case 17. Lead II. A and B. Sinus tachycardia with slowing. C. Nodal rhythm. D. Idioventricular rhythm. E. Abnormal ventricular complexes. F. Epinephrine given with resultant short run of very abnormal ventricular beats.

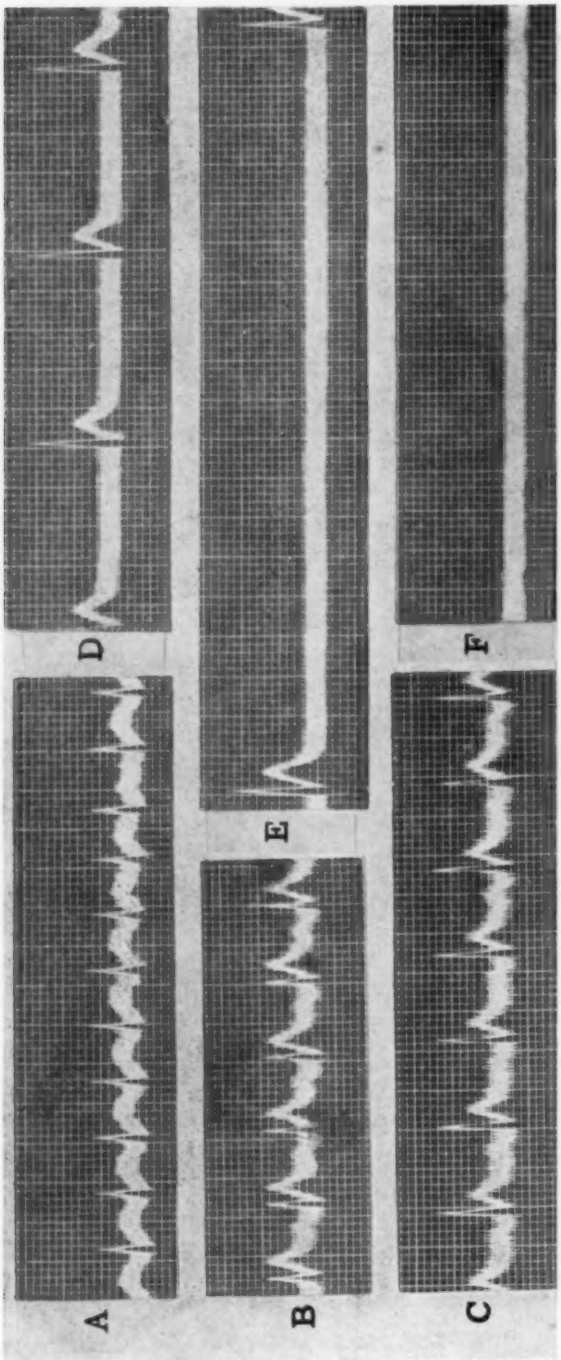

FIG. 7. Sequence of events in case 18. Lead II. A, B, C, and D. Sinus rhythm with progressive slowing. E. 3 to 1 A-V block. F. Terminal auricular beats. Epinephrine given without effect.

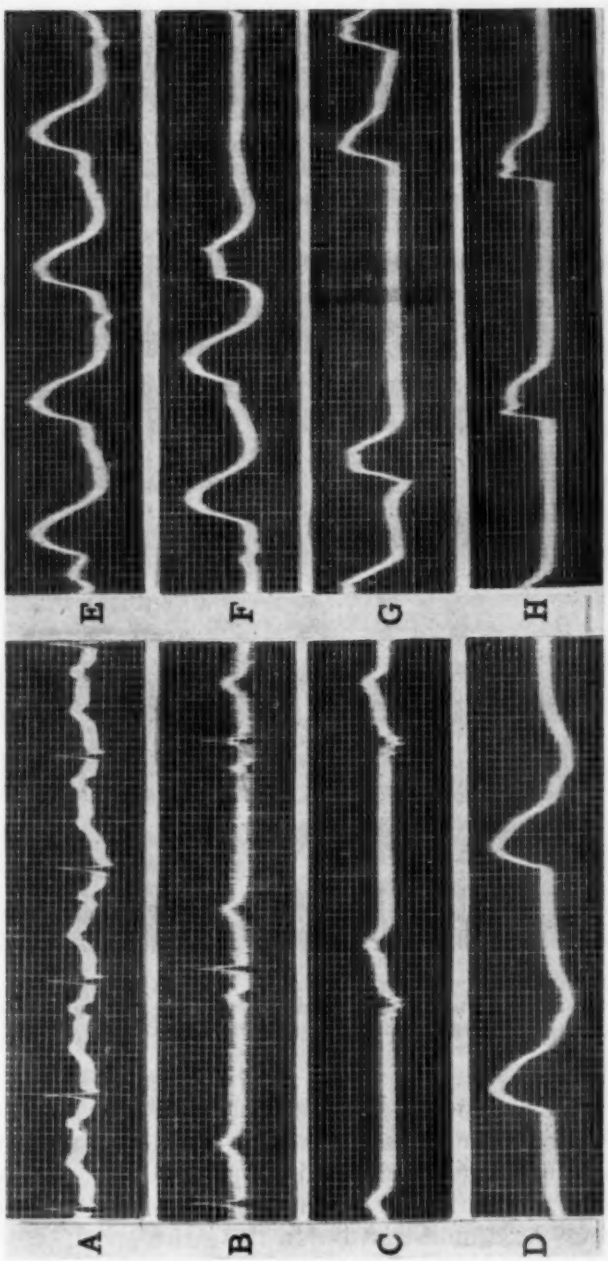

FIG. 8. Sequence of events in case 24. Lead II. A. Sinus tachycardia. B. Sinus bradycardia. C. Nodal rhythm. D. Idioventricular rhythm with very abnormal ventricular complexes. E. Epinephrine given with change to sinus rhythm. F, G, and H. Continuation of ventricular complexes for 36 minutes after cessation of respiration.

Effect of Intracardiac Epinephrine

The 18 cases of the series in which epinephrine was injected into the heart in the study of cardiac resuscitation are worthy of special consideration. Table 2 presents a summary of the results obtained from intracardiac epinephrine. In 10 patients the adrenalin was injected directly into the ventricular chamber and in one case it was put into the right auricle. In nine instances it was injected presumably into the ventricular myocardium. In two of the 18 cases the epinephrine was initially placed in the cardiac cham-

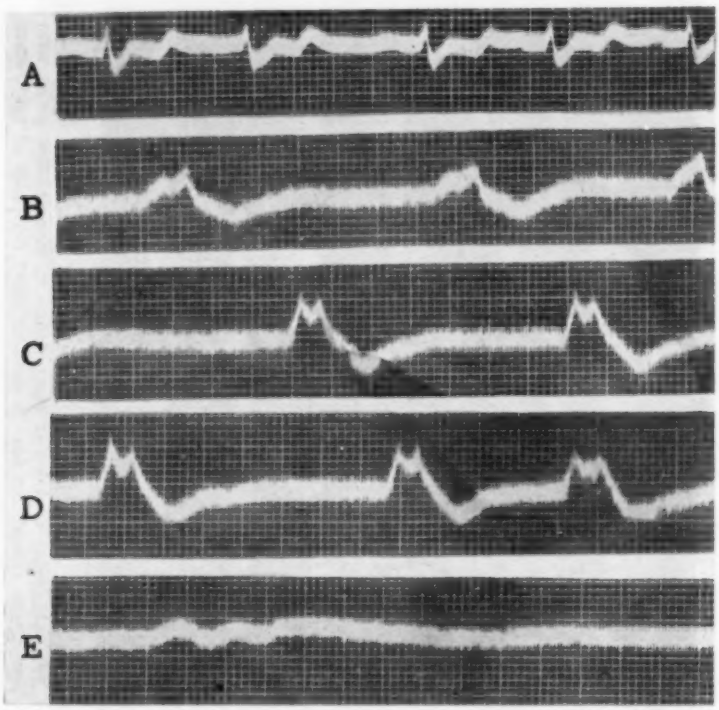

Fig. 9. Sequence of events in case 26. Lead II. A. S-type bundle branch block. Between A and B, cardiac standstill occurred and epinephrine given into cardiac chamber without effect. Epinephrine then given into myocardium, and B, C, D, and E show the resultant ventricular beats which persisted for 1.5 minutes.

ber and when no effect was noted, an additional injection was made into the myocardium with production of a few ventricular extrasystoles in one instance and ventricular flutter and fibrillation in the other. Care was exercised to notice whether the injection of the needle alone in five cases had any effect and none could be demonstrated. In the entire group of 18 patients only seven showed a response to the epinephrine injections including five of nine cases (56 per cent) submitted to myocardial infiltration with adrenalin and only two of 11 cases (18 per cent) treated by injection into the cardiac chambers. Of the total of seven patients in whom an effect was obtained,

the injection produced ventricular fibrillation in three instances and ventricular extrasystoles in two cases and restored the regular ventricular beats in the other two patients in one of whom the beats continued for 36 minutes after respiration had ceased. Figures 6 to 11 demonstrate the effects encountered with intracardiac and myocardial injections of epinephrine.

Discussion

The factors of age, sex, clinical findings, primary disease, precipitating cause of death, presence or absence of heart disease, or anemia, and findings at autopsy appeared to have no conditioning effect on the mechanism of death judging from the electrocardiographic manifestations. The findings in our

Table II

Summary of Results from Intracardiac Epinephrine

Case No.	Epinephrine in Cardiac Chamber	Epinephrine in Myocardium	Result
3	Yes	—	No effect
10	—	Yes	No effect
13	Yes	—	No effect
14	Yes	—	No effect
17	Yes	—	Ventricular extrasystoles for 8 seconds
18	—	Yes	No effect
20	—	Yes	Ventricular flutter and fibrillation
22	—	Yes	Restoration of original sinus rhythm
23	Yes	—	No effect
24	Yes	—	Restoration of original sinus rhythm
25	—	Yes	No effect
26	Yes	Yes	No effect from injection into chamber. Myocardial injection produced ventricular extrasystoles for 1.5 minutes
27	Yes	Yes	No effect from injection into chamber. Myocardial injection produced ventricular fibrillation
28	—	Yes	No effect
29	Yes	—	No effect
30	Yes	—	No effect
31	Yes	—	No effect
33	(right auricle)	—	No effect
34	—	Yes	Ventricular flutter and fibrillation

series do not differ significantly from those reported by previous investigators. Although initial sinus acceleration often occurred, a conspicuous slowing of cardiac rate just before death was a most constant finding. Almost just as frequent was the occurrence of increasing auriculoventricular and intraventricular conduction times as death ensued. Ventricular fibrillation was the terminal rhythm in approximately 26 per cent of cases.

From the physiologic point of view the initial sinus acceleration is due primarily to transient sympathetic nerve irritability. Very shortly before death the vagus centers in the medulla are apparently stimulated producing in practically every terminal heart, a marked vagotonic state resulting in sinoauricular node and auriculoventricular conducting bundle depression. The fundamental factors of toxemia, asphyxia and local nutritional changes

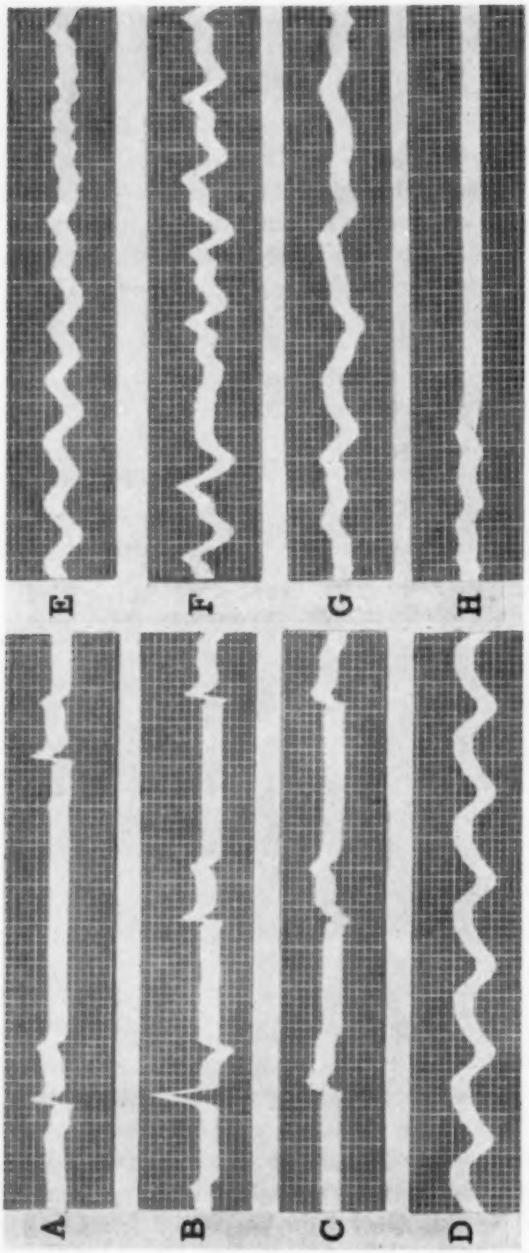

FIG. 10. Sequence of events in case 27. Lead II. A. Sinus bradycardia. B. Ventricular extrasystole. C. Idioventricular rhythm. D. Ventricular flutter. E. Ventricular fibrillation. F. Epinephrine given into cardiac chamber without effect. Epinephrine given into myocardium with resultant ventricular fibrillation shown in F, G, and H.

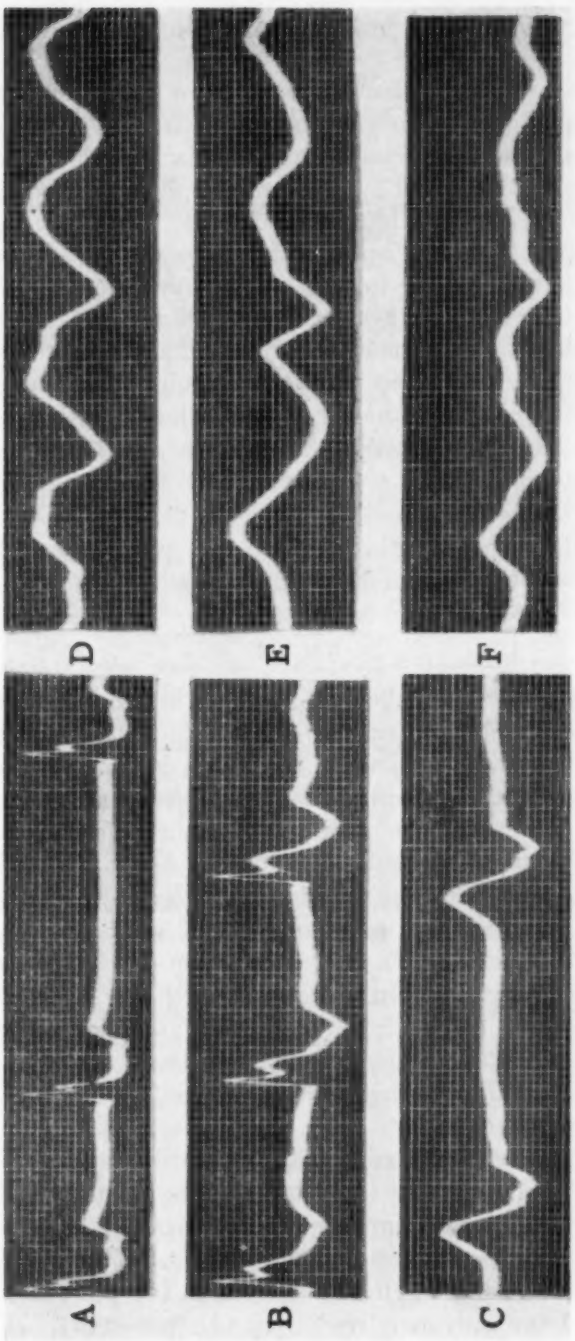

FIG. 11. Sequence of events in case 34. Lead II. A and B. Auricular fibrillation. C. Complete A–V block. D, E, and F. Epinephrine given into myocardium with resultant ventricular flutter and fibrillation.

in addition produce transient focal and local points of heightened irritability particularly in the ventricular myocardium and only infrequently in the auricular wall.

Intracardiac epinephrine following cessation of the cardiac beat produced only infrequent and usually insignificant responses. Only in seven of 18 patients so treated was there some sign of cardiac resuscitation and in five of these the effect was produced by myocardial infiltration and in two others by injection into the cardiac chambers. In only two of the patients was there a restoration of the original ventricular beats for a significant time whereas the others suffered the initiation of terminal ventricular fibrillation or ventricular extrasystoles. It appears not unlikely that if the patients in this series had not been so chronically and terminally ill, intracardiac epinephrine preferably given into the myocardium might have been more successful. Furthermore, unlike the procedure followed in this investigation it would appear that the intracardiac epinephrine to be life saving should be given if at all possible before complete cardiac cessation when the heart muscle and vital cerebral centers have not been deprived of oxygen for too long a period. Resuscitation otherwise becomes quite impossible because of the fatal and irreversible changes due to anoxemia.

Summary

Electrocardiograms were taken on 34 cases before, at the time of, and after clinical death. Slowing of the cardiac rate was almost a constant finding with subsequent sinoauricular node depression and resultant auriculoventricular nodal rhythm appearing in over one third of the cases. Auriculoventricular and intraventricular block in various degrees was extremely common. Evidences of ventricular irritability were manifested by the frequent occurrences of ventricular fibrillation, tachycardia and flutter along with ventricular extrasystoles from single and multiple foci. Auricular fibrillation did not appear terminally except in those instances where it had been present previously. The terminal complex in the electrocardiogram represented ventricular activity in 27 cases and auricular activity in seven. The terminal ventricular complexes often assumed bizarre shapes with marked variation in form, amplitude, duration, and with considerable slurring.

Attempts at cardiac resuscitation with intracardiac epinephrine following cessation of heart activity were made in 18 cases including 11 attempts in which the drug was injected into the cardiac chambers and nine in which it was infiltrated into the ventricular myocardium. The latter method was more successful, producing an effect in five cases (56 per cent) whereas the former accounted for only two responses (18 per cent). The resultant rhythms included three instances of ventricular fibrillation, and two of ventricular extrasystoles; in only two patients was there restoration of regular

ventricular beats in one of whom the cardiac activity continued for 36 minutes after respiration had ceased.

The authors gratefully acknowledge their appreciation to Miss Edna Edwards, Mrs. Dorothy Marsden and Miss Wanda Wilson for their technical assistance.

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LABILE DIABETES: ELECTROENCEPHALOGRAPHIC STATUS AND EFFECT OF ANTICONVULSIVE THERAPY *

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IN a study of spontaneous hypoglycemia associated with electrocerebral dysfunction [1] emphasis was laid on the similarity of symptoms in both conditions for which reason their coexistence may be overlooked. It was also shown that in such patients the clinical manifestations of hypoglycemia may develop in absence of critically low blood sugar levels, and it was assumed that when both conditions are operative in the same subject the threshold for the development of clinical reactions is decreased. Finally, it was found that the patients respond remarkably well to therapy which, in addition to management of hypoglycemia, includes the use of anticonvulsant medications.

The peculiar features of hypoglycemic reactions in labile diabetes, namely their frequency and severity and the suddenness of their onset, suggest a state of unusual reactivity to insulin or to fluctuations of the blood sugar and make it conceivable that factors other than mere depression of the blood sugar may be responsible for hypoglycemic manifestations in this type of diabetes. Thus a certain analogy could be drawn regarding the mechanism underlying the hypoglycemic complex in both spontaneous hypoglycemia and labile diabetes. With this idea in mind we have undertaken to study in the latter condition the configuration of the brain waves pattern as well as the relationship between insulin reactions and glucose concentration in the blood. We were also anxious to investigate the possible use of anticonvulsants in unstable diabetes.

The term "labile diabetes" has not been well defined in the literature. Its more or less synonymous use with the term "juvenile diabetes" stems from observations made in children whose diabetes is characterized by frequent incidents of hypoglycemia alternating with acidosis and coma. In this presentation the term labile diabetes refers to that group of diabetics who, regardless of age, time of onset and duration of disease, exhibit a very narrow time-margin between excessively high and critically low blood sugar values, and who in consequence show rapid transitions from hypoglycemia and aglycosuria to massive glycosuria and acidosis. In these patients small amounts of insulin used during episodes of heavy glycosuria often produce a rapid fall of the blood sugar to hypoglycemic levels; but if no additional insulin is given the sudden development of acidosis may not be averted.

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Clearly, labile diabetes is considerably distressing to the patient and its management imposes a great burden on the physician.

Material and Procedure. A group of seven labile diabetics with no family history of epilepsy and no history of convulsive seizures prior to the onset of diabetes, was studied. Blood sugar determinations and urinalyses for sugar content in casual as well as 24 hour specimens were made at least once a month. Whenever possible, blood sugar determinations were also done in the course of hypoglycemic manifestations or at the time the patients complained of signs of oncoming reactions. On several occasions the tests were repeated after an interval of one to two hours during which interval food was withheld in spite of subjective and objective signs of insulin reactions.

Electroencephalograms were taken by means of the three-channel Grass instrument. Both the bipolar and monopolar systems of recording potential variations from the brain were utilized. Electrodes were placed over the prefrontal, motor, parietal and occipital regions of the head bilaterally; indifferent electrodes were applied to the ear lobes. After a preliminary resting record was obtained patients were routinely hyperventilated for a period of two minutes. The criteria for determining abnormal activity depended upon the presence of slow potentials, high amplitude fast potentials and irregular or disorganized patterns. In order to avoid the effect of low blood sugar concentrations the electroencephalograms were taken after a normal meal (breakfast or lunch).

The effect of anticonvulsants was studied in three cases. Periods of five to 33 days during which anticonvulsive therapy was discontinued were interposed to serve as controls. Control electroencephalograms were taken in two patients after 12 and 17 months of treatment.

Case Reports

Case 1. A 44 year old man, a college professor, was first seen in October 1942. He developed diabetes at the age of thirty-four. On a low carbohydrate, high fat diet with two doses of regular insulin daily he felt continuously weak and tired and had frequent insulin reactions alternating with glycosuria. Accused by his physicians of breaking the diet, he felt humiliated and compelled to do without medical advice. For eight years he made his own experiments in raising the dietary carbohydrates, but finally because of frequent insulin reactions and a state of constant fatigue he consulted a physician who prescribed a diet of 300 gm. of carbohydrates with an insulin dosage of 70 units of protamine-zinc and 14 units of regular insulin. On this regimen the patient felt somewhat better and gained some weight but his diabetes could not be satisfactorily regulated. From the very onset the patient's symptoms and laboratory findings were characteristic of unstable diabetes. He had frequent manifestations of an overdose of insulin ranging from mild paresthesias to severe reactions with retrograde amnesia, as well as periods of hyperglycemia accompanied by heavy glycosuria. To overcome reactions he took food in excess of the prescribed diet and was gaining weight constantly. In 1940, for instance, his weight rose from 137 to 163 pounds, a gain of 26 pounds in one year. He had a rapid pulse rate for years, but the basal metabolic rate was found on several occasions to vary from

minus 10 to minus 14 per cent, and the electrocardiograms were normal. There was also a change of personality manifested by extreme anxiety, depression, episodes of impulsiveness and restlessness as well as mental sluggishness which interfered with his professional work. To combat these neuro-psychiatric manifestations he took phenobarbital and B-complex capsules but because of lack of response he was finally given up as a case of hypochondriasis.

To prevent this patient from having his daily reactions a gradual reduction of insulin was made and he was placed on a constant diet of 230 gm. of carbohydrates, 70 gm. of protein and 75 gm. of fat. However, his diabetes remained uninfluenced and as chaotic as before. In January 1943, for instance, for a period of 10 days he was subject to reactions with only 40 units of protamine-zinc insulin, then developed marked glycosuria which necessitated an increase in the dosage to 48 units of protamine-zinc and 10 units of regular insulin. For short periods of time he seemed to be regulated on 40 to 54 units of insulin with a diet of 240 to 260 gm. of carbohydrates, while on other occasions reactions would increase in frequency and severity on as little as 8 or even 5 units of protamine-zinc insulin. The amount of sugar in the urine was also subject to considerable variation.

Because of frequent reactions, on three occasions it was necessary to take him off insulin for periods varying from three to 10 days. Strangely, even when no insulin was taken he still complained of reactions and continued to consume large amounts of carbohydrates. During one of these periods without insulin, for instance, he took one day in addition to his diet, some 400 gm. of carbohydrates seemingly without much effect.

TABLE I

Blood Sugar Values during Reactions In Case 1

Date	First Blood Sugar Reading	Second Blood Sugar Reading 2 Hrs. Later
August 18, 1943	187 mg. per cent	
November 11, 1944	300 mg. per cent	214 mg. per cent
December 9, 1944	318 mg. per cent	200 mg. per cent
February 17, 1945	217 mg. per cent	187 mg. per cent
March 10, 1945	217 mg. per cent	178 mg. per cent
September 8, 1945	221 mg. per cent	148 mg. per cent
October 13, 1945	360 mg. per cent	190 mg. per cent
January 8, 1946	286 mg. per cent	226 mg. per cent

The concentration of sugar in the blood also showed extreme lability with rises and falls occurring with great rapidity. However, a more detailed study of reactions revealed that clinical symptoms usually attributed to an excess of insulin frequently occurred at high blood sugar values. Readings obtained on several occasions while he exhibited moderately severe reactions are presented in table 1.

Throughout a period of four years different plans of insulin administration were used. The ones that seemed to yield some results at one time were usually found at another time to be of no benefit to the patient.

Because of the extreme lability of the patient's diabetes, and because his reactions seemed unrelated to blood sugar variations, an electroencephalogram was taken on June 17, 1946. This revealed several long bursts of 2 to 3 cycle per second activity over the right frontal area. Hyperventilation did not appreciably alter the pattern. The tracing was interpreted as suggestive of an epileptogenic focus in the right frontal area (figure 1).

The patient was first given for five days tridione which he did not tolerate well, then dilantin which he took continuously for four weeks. In the following five months, i.e., from the beginning of August to the end of December 1946, five control periods without dilantin varying from seven to 15 days were interposed. During

control periods he remained fairly well for only five to seven days. Whenever the test period was continued beyond a week reactions became quite frequent and distressing. On one occasion on the eleventh day without dilantin he "was up all night with definite shocks," took 50 gm. of carbohydrates without relief, reduced the insulin dose on the next day, but was unable to stop the reactions. Being very cooperative and much interested in this study, he was anxious to continue the experiment, but decided that he could no longer do without dilantin. The drug was re-

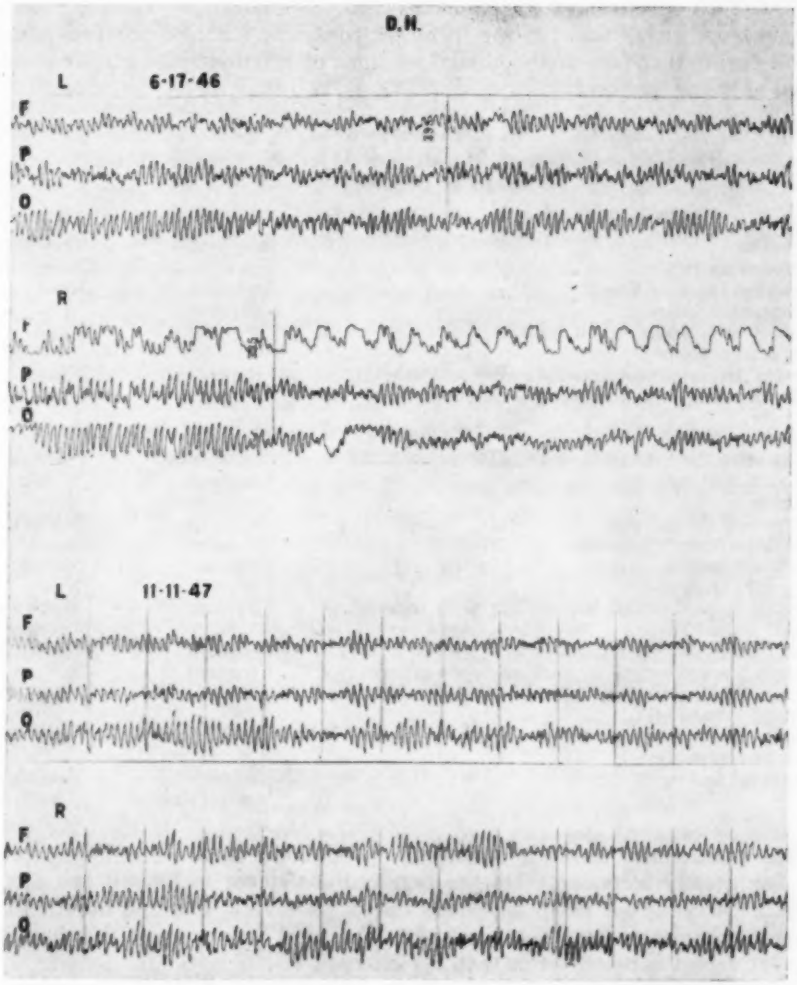

FIG. 1. Initial and control electroencephalograms in Case 1.

sumed on the twelfth day of the control period and the reactions became milder and less frequent and subsided entirely within three days. Recently dilantin was gradually replaced by mesantoin which for the past six months was taken for periods of 10 days with rest periods of three to five days. Except for drowsiness and a slight depression during the first two weeks on mesantoin the medication was well tolerated. The patient remains free from severe and moderately severe reactions and is subject

to infrequent and very mild reactions. Their onset is slow and gradual in contrast to their precipitous onset in previous years and they yield easily to small amounts of carbohydrates. He seems to be stabilized on 22 units of protamine-zinc and 20 units of regular insulin. Most of the time he is sugar free and his blood sugar is maintained in the normal range. Since the anticonvulsant treatment was initiated 14 blood sugar determinations showed variations from 120 to 200 mg. per cent and only on two occasions, when he had a cold, were higher values of 208 and 210 mg. per cent obtained.

To test his reactiveness to low blood sugar concentrations, on one routine visit when his blood sugar was 120 mg. per cent food was withheld for two hours. He felt well during that time and exhibited no signs of reaction although his blood sugar dropped to 95 mg. per cent.

TABLE II

Description of Experiences without Dilantin and during Dilantin Therapy as Reported by Case 1

Nature of Experience	Without Dilantin	While on Dilantin
Mild shocks	Frequent	Very few
Pronounced shocks	A few	None
Very sudden onset of shock	Frequent	None
Disturbance of vision	Frequent	None
Shock-like symptoms when number of urine tests show heavy sugar	Frequent	None
Associates' comment on unusual pallor or flush	Frequent	None
Periods of weakness and fatigue without previous exertion	Frequent	None
Sweating in absence of exertion	Frequent	None
Tingling sensation in hands and feet	Occasional	None
Cold hands and feet	Frequent	Seldom
Headaches	Occasionally	None
Boredom and drowsiness	Frequent	Seldom
Uncalled-for anger responses	Frequent	None
Self-pity tendencies	Frequent	Seldom
Pronounced anxiety	Frequent	None
Periods of impulsiveness alternating with indecisiveness	Frequent	Much more smoothed out
Elation alternating with depression	Frequent	Smoothed out
Tendency toward errors in various types of manipulations (e.g. mathematical work, speech, painting, writing, games, etc.)	Frequent	Seldom
Difficulty in beginning, or once begun persisting in work or recreation	Pronounced	Very mild
Background feeling	Uneasy—what's next?	Feeling of well-being

The patient also shows a remarkable psychologic improvement. His ability to work has greatly increased. He has regained confidence in himself and has no difficulty in carrying out his professional duties. He feels that the improvement evidenced in laboratory data "does not reflect the great improvement that has occurred. My inner report is much better than my charts."

A control EEG taken after 17 months of treatment shows a borderline tracing with no features suggestive of an epileptogenic focus. High voltage 8.5 to 9 cps rhythm dominates in all leads and only a few 8 cps potentials are observed (figure 1).

The favorable effect of anticonvulsive therapy in this case is best illustrated by the patient's own comparison of symptoms which he exhibited for years with the improvement noticed shortly after the treatment was begun (table 2).

Case 2. A young woman, aged 31, unmarried, developed diabetes at the age of twenty-four. The onset of her diabetes was extremely sudden, practically a matter of less than 24 hours with polyuria coming on unexpectedly one day and nocturia the

following night. The patient remembers distinctly that during that night she had to get up seven times to pass water. Her diabetes was diagnosed two weeks later. She was placed on a restricted diet with three daily injections of crystalline insulin. Within less than four months her weight dropped from 142 pounds to 119. She was then given a liberal diet with 300 to 390 gm. of carbohydrates, 95 to 130 gm. of protein and 60 to 100 gm. of fat, with a daily insulin dosage of 64 to 92 units of protamine-zinc and 9 to 18 units of regular insulin. On this regimen her weight rose rapidly to 155 pounds and she felt much stronger. From the beginning of insulin therapy she was subject to frequent severe reactions, particularly at night and upon arising in the morning. The reactions were often associated with loss of consciousness and she had to be fed sugar forcibly by her family. She was unable to work, became depressed, and although a very popular girl before she developed diabetes, she avoided people and lived almost like a recluse.

When first seen at the age of 26 her height was 70.5 inches and her weight 144.75 pounds. She complained chiefly of insulin reactions and extreme tiredness. Menstrual periods were delayed for two or three months and very painful. On one occasion shortly after the onset of diabetes, she had not menstruated for nine months. She often ran a series of insulin shocks during periods as well as during the time of anticipated and missed periods. Physical examination was negative except for hypotension and chronic acne of the face. The basal metabolic rate was minus 23 per cent. There was no family history of diabetes nor epilepsy, no history of head injury nor convulsions in the patient's infancy.

Because of frequent and incapacitating insulin reactions the patient was compelled to take extra carbohydrates almost every day. It was thought that with less insulin she might be able to avoid reactions and keep her diabetes under better control. To this end, in the first eight months of treatment insulin was gradually reduced to 42 units of protamine-zinc and 10 units of regular, while the diet was kept constant at 240 gm. of carbohydrates. However, in spite of the constancy of diet and insulin, she continued to have daily reactions alternating with heavy glycosuria. On one occasion, for instance, she was shocking all day, then suddenly before midnight developed polyuria with massive glycosuria. At another time a series of hypoglycemic reactions came on shortly after lunch and though she ate every half hour for some five hours, she remained sugar free with no relief from most severe headaches. An intravenous administration of glucose had no effect, and the headaches subsided

TABLE III

Variations in Sugar Excretion during the Night in Case 2

Date	Amount of Sugar	Remarks
1943 November 13	61 gm.	Severe reaction on the previous day
27	12 gm.	Reaction at 11:00 a.m. same day
29	6 gm.	
30	10 gm.	
31	2.3 gm.	
December 30	5 gm.	
1944 January 20	0.7 gm.	
21	9 gm.	
22	±	
February 18	22 gm.	
March 19	4 gm.	Blood sugar 250 mg. %
21	38 gm.	
22	30 gm.	
23	3 gm.	
24	1.8 gm.	
26	11 gm.	
27	1 gm.	
April 1	24 gm.	

only after another glucose injection 20 minutes later. However, within a half hour heavy glycosuria appeared, so that scarcely an hour after the intravenous administration of glucose she had to be given insulin.

Since the most serious reactions occurred upon arising, to prevent them the morning glycosuria had to be tolerated. Urine specimens covering the period from bedtime until morning showed great variations in sugar content as may be seen from table 3. The sugar excretion during the day was also most irregular. On some days she remained sugar free the whole forenoon while on others the urine was loaded with sugar. At times her diabetes improved for no apparent reason so that for a few weeks there was little sugar in the urine and only a few mild reactions.

Blood sugar specimens usually taken one and a half to two and a half hours after breakfast showed over a period of three and a half years a wide range of variations from 95 to 378 mg. per cent. Also, there was no parallelism between the blood sugar values and the amounts of sugar excreted as may be seen from table 4.

Just as her diabetic condition, so also her weight showed marked fluctuations. At times it remained stationary for months; then for no demonstrable cause it would drop in a few days by 8 to 10 pounds and remain again unchanged for weeks or months.

Various insulin mixtures were used without much effect, and the only valuable result was obtained by a reduction of the morning insulin dose so that additional insulin could be taken during the day if necessary. In this way the patient was able at least to keep free from severe shocks on arising. In November 1944 globin insulin was given a trial. At first she had globin insulin alone, but soon to check the heavy

TABLE IV

Comparison of Blood Sugar Values with the 24 Hr. Sugar Excretion in Case 2

Date	Blood Sugar	Sugar in 24 Hr. Specimens
1942 October 30	142 mg. %	25 gm.
1943 April 17	166 mg. %	29 gm.
July 2	220 mg. %	115 gm.
August 3	250 mg. %	6.6 gm.

morning glycosuria protamine-zinc insulin was added very cautiously. A dosage of 20 to 22 units of protamine-zinc with 20 to 22 units of globin insulin was finally adopted and in addition she took regular insulin during the day whenever necessary. On this regimen she felt more secure although her diabetes remained basically unchanged. She still had to take up to 38 additional units of regular insulin on some days and none on others, and she continued to show sudden changes from hypoglycemic reactions to hyperglycemia with massive excretion of sugar and extreme exhaustion.

Gynecological examination by two competent specialists revealed no pelvic disease. To control the dysmenorrhea and oligomenorrhea they suggested various combinations of hormonal therapy. We tried estrogens by mouth and parenterally, luteal hormone alone or in conjunction with estrogens (Dipro), gonadotropin, and thyroid extract in a dose of one half to two grains a day. The response of her diabetic condition to hormonotherapy was most chaotic. On stilbestrol, for instance, the insulin requirement was reduced and the frequency of reactions diminished on some occasions, while on others there was heavy glycosuria accompanied by tiredness and loss of weight. Corpus luteum therapy usually caused an increase in glycosuria, whereas Dipro injections were followed by glycosuria and polyuria, except for one instance when there was less spilling of sugar on Dipro.

Likewise, no constant relationship could be found between menstrual periods and the diabetic state. Most of the time she ran a series of reactions during the first few menstrual days, but in June 1944 she required more insulin during the first menstrual

day and much less on the last day of the period as well as during two postmenstrual days. At times hypoglycemic manifestations came on during the six to ten premenstrual days and were succeeded by glycosuria and increased insulin requirement at the onset of the period and by recurrence of reactions at the end. At other times heavy glycosuria preceded the period by three days, necessitating almost double the usual amount of insulin. On the whole, the insulin requirement around and during the periods changed most rapidly and unpredictably. On one occasion, for instance, while she was doing relatively well for some 10 days on 20 units of protamine-zinc and 34 units of regular insulin with additional 5 to 6 units of regular insulin in the afternoon, she excreted large amounts of sugar on the first menstrual day, had continuous reactions all of the second day, again needed more insulin on the third day. Then she felt fairly well for the next three days, but reverted to heavy glycosuria during the three postmenstrual days.

On June 26, 1946, an electroencephalogram was taken. The tracing showed moderate voltage 10 cps alpha rhythm with occasional trains of low to moderate amplitude fast activity and some irregularities in wave contours. Hyperventilation resulted in a few 6 to 8 cps potentials. The record was reported as a borderline tracing.

Tridione was chosen as the first anticonvulsant drug to be tried in this case. After a preliminary period of 11 days during which the patient had only one mild reaction and needed additional 6 to 8 units of regular insulin on three days, the drug was given for seven days, namely, from the sixteenth to the twenty-second intermenstrual days. While taking tridione she had several mild reactions on the first day and frequent severe shocks without loss of consciousness on the second, fourth and fifth day. A marked glycosuria occurred on the third, sixth and seventh days and could not be controlled even with 30 additional units of regular insulin. The patient felt very depressed and so weak that she could hardly get out of bed. From the third day on tridione she felt blinded in the sun and had the sensation of seeing objects lose their shape and identity in an intense blur of light. On the whole, on tridione she was decidedly worse—"never in my whole life have I felt so rotten."

Dilantin was begun 11 days after the next menstrual period, after a lapse of 17 days during which heavy glycosuria occurred only once. The drug was taken continuously for 55 days. During the first 42 days there were only two mild reactions and only small additional doses of insulin (from 8 to 10 units) were needed on nine days. During the next menstrual period she had three mild reactions and no additional insulin was required. Then because of intermittent aphthous stomatitis dilantin was discontinued and soon the rate of reactions increased and additional doses of insulin were more frequently used. After 48 days without dilantin the drug was resumed, and for over nine months it was taken regularly for periods of 10 to 17 days with rest periods of five to seven days. During the first few days on dilantin the need for insulin was markedly reduced and she had four severe reactions followed by glycosuria of one day's duration. But soon thereafter her diabetes seemed to be more stabilized with few mild reactions and infrequent incidents during which 6 to 8 additional units, and only once 10 units of regular insulin were needed. On several occasions she remained entirely free from reactions for over three weeks. During two control periods of 10 and 32 days without dilantin, only a few mild reactions occurred near the menstrual periods (four mild and one moderately severe reaction during the one month control period). The insulin requirement remained more stable even in the course of menstrual periods.

Dilantin proved particularly valuable for the control of reactions. During a six months' period before the treatment was begun, the patient had a total of 48 days in which reactions occurred, while in the six months' period with dilantin 25 such days were noted. During the same six month period there were 17 severe reactions

when no medication was taken, as against four severe reactions since the treatment with dilantin was inaugurated. Furthermore, on dilantin the onset of reactions was smoothed out and gradual so that the patient found it easier to cope with them, while before this therapy reactions occurred mostly without warning and rapidly grew deep.

The effect of dilantin on the blood sugar was also significant. Of 15 determinations, 13 showed variations from 107 to 200 mg. per cent; one was 245 mg. per cent on the third day of menstruation and another one 235 mg. per cent two days after a period. An improvement was also noted in the patient's general condition. Her weight rose to 143 pounds and remained stationary for over nine months. She also shows a good psychologic adjustment. In her own words "dilantin is a miraculous drug."

In the past three months the patient was gradually changed over to mesantoin with results as good as those obtained with dilantin.

Case 3. A married woman aged 33 years, a writer by profession, was first seen in September 1942. She was well until 1940 when because of her mother's death and her husband's business difficulties she became greatly depressed, lost interest in her family, and began to lose weight rather rapidly (she recalls losing some eight pounds in one week). A psychiatrist advised psychoanalytical treatments, but the patient could not accept the idea that she herself would be unable to overcome her personality disorders. As her condition did not improve, three months later she submitted to psychoanalysis. Supposedly two days after the first treatment she developed polyuria and nocturia and shortly thereafter sugar was found in the urine. At first she was placed on a 900 calorie diet, but continued to lose weight, felt weak, and had bouts of excessive perspiration. Pulmonary tuberculosis was then suspected but ruled out in view of negative laboratory findings. At the end of the first year of treatment her diet was slightly enlarged and she was given 5 to 10 units of regular insulin daily. She soon began to suffer from frequent insulin reactions, was unable to attend to her work and was on the verge of suicide. She then consulted another physician and was given a diet of 250 gm. of carbohydrates, 80 gm. of protein and 70 gm. of fat, with 36 to 40 units of protamine-zinc and 10 to 14 units of regular insulin daily. Her diabetic difficulties can be summed up as follows: She was afraid of glycosuria and tried hard to keep her urine sugar free. In this she was not successful as the addition of small amounts of insulin (4 to 8 units) to combat a heavy glycosuria would bring on reactions within a few hours. In consequence, there were periods of sugar free tests accompanied by continuous tiredness and frequent moderately severe insulin reactions interspersed with periods during which she excreted large amounts of sugar. On several occasions the 24 hour specimens contained up to 60 gm. of sugar and more. During the premenstrual week she always had more sugar in the urine and felt extremely tired, nervous and depressed, frequently had a feeling of inward trembling and tightness in the neck, and her sleep was restless. With the onset of menstrual bleeding these symptoms would subside and frequent reactions would appear even with a reduced insulin dosage. She learned to take more insulin before her periods and lower the dose markedly with the onset of the flow, but even so she was unable to control the described sequence of events. She also gave a history of anxiety for which she had been psychoanalyzed for the past three years.

Thirty-three blood sugar determinations made between September 1942 and October 1946 showed variations from 127 to 260 mg. per cent. On two occasions the blood sugar concentration was low (69 mg. per cent); on one occasion it reached 308 mg. per cent. In September 1946, for no apparent reason insulin reactions became more frequent and severe; they lasted longer than usual and did not yield easily to ingestion of carbohydrates. At this point (September 30, 1946) an electroencephalogram was taken. This revealed moderate to high amplitude 11 cps rhythm

with some admixture of fast activity. There were frequent random 6 to 8 cps potentials and occasional 5 cps potentials. Hyperventilation produced hypersynchronous discharges of 5 to 6 cps rhythm in all leads. The tracing suggested a generalized cerebral disturbance of physiologic nature, but it could also be considered as consistent with a convulsive tendency (figure 2).

Dilantin was then prescribed for periods of 10 days with rest periods of five days and the patient improved considerably. There was a better adjustment to insulin

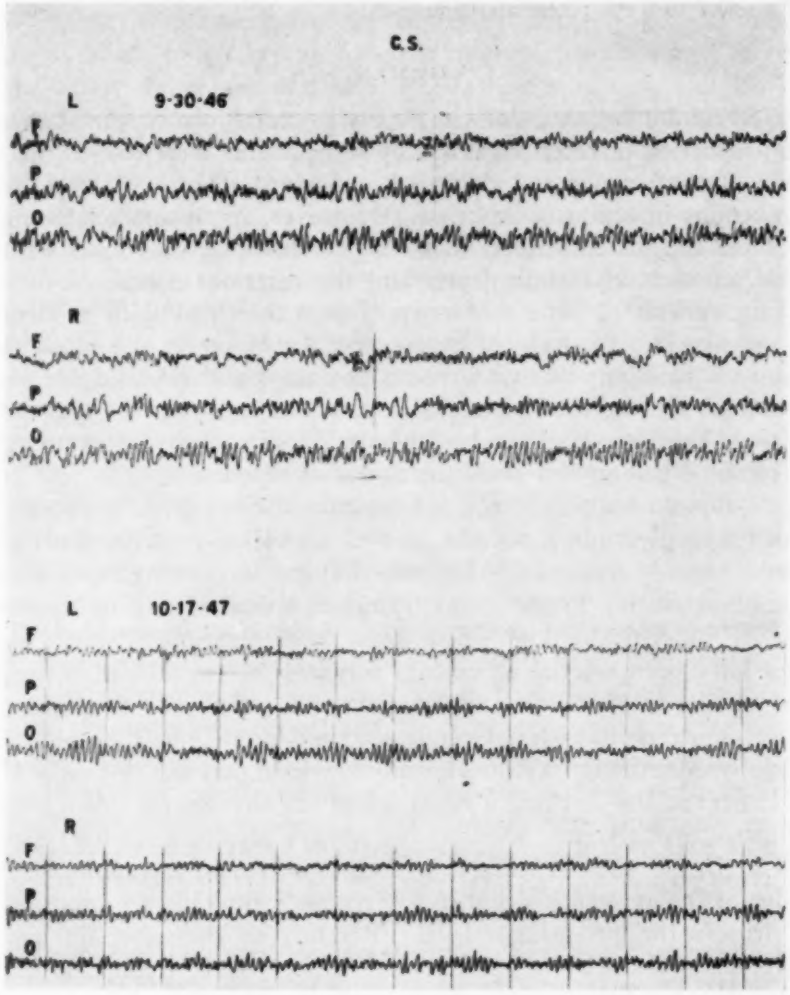

FIG. 2. Initial and control electroencephalograms in Case 3.

as evidenced by absence of reactions although the dose of insulin remained practically unchanged. In the patient's own words, she is now "less sensitive to insulin, not so prone to insulin reactions, and has a feeling that her diabetes is now a controlled thing." The premenstrual tension, depression and heavy glycosuria have also subsided. Moreover, she shows a remarkable psychologic improvement. She feels less restless, mentally more even, and has "far less anxiety in approaching things

in general." In the past 12 months during which dilantin was taken, the blood sugar concentration varied from 80 to 182 mg. per cent; on one occasion it was 61 mg. per cent and on another 236 mg. per cent. In November 1946 she took no dilantin for 10 days and her blood sugar rose to 266 mg. per cent. Again, she was without the medication for 14 days in February 1947 and in the last six days of that period her nervousness recurred and the reactions became quite frequent. A control electroencephalogram taken in October 1947 showed no definite abnormality. It was free from previously noted random 5 to 8 cps potentials and hyperventilation resulted in only a few 7 to 8 cps potentials (figure 2).

Comment

1. Correlation between Clinical Reactions and Blood Sugar Values. A certain proportion of reactions noted by our patients were due to the hypoglycemic effect of insulin and yielded to oral administration of carbohydrates or intravenous injection of dextrose. However, in an appreciable number of instances the patients were unable to combat reactions even with considerable amounts of carbohydrates and the reactions continued for unusually long periods of time. Moreover, they coincided with moderate or heavy glycosuria. A study of glucose concentration in the blood during such unusual reactions was undertaken in Case 1 and revealed surprisingly high values. During the two hours of observation the blood sugar failed to fall to pathologic low levels and neither intake of carbohydrates nor abstinence from food had any effect on the course of reactions.

The symptom-complex which accompanies various types of experimental or clinical hypoglycemia is not always well correlated with the depression of the blood sugar. Appreciably low blood sugar levels may remain asymptomatic [2-14] while the hypoglycemic symptom-complex may be encountered in absence of critically low blood sugar concentrations.[1, 4, 15-19] Various theories have been offered to explain this lack of parallelism between the clinical and laboratory status of hypoglycemia. The one that has gained wide acceptance is that hypoglycemic reactions occur when the blood sugar falls rapidly even though a pathologically low level may not be reached.[6, 13, 15, 20, 21] However, the fact that a rapid fall of the blood sugar from very high to distinctly hypoglycemic levels is not always accompanied by symptoms[6] as well as the fact that critically low levels may remain asymptomatic negate the value of the assumption that hypoglycemic symptoms are produced by a sharp drop in the blood sugar level. Recently in discussing our paper on hypoglycemia, Himwich suggested that hypoglycemic manifestations may result from a low brain sugar which might not be reflected in the systemic blood.[22] In extension of this concept it is conceivable that even with normal availability of glucose in the brain there may be some disturbance in the uptake or utilization of sugar by the brain, thus depriving this tissue of its main nutritive substance.

The blood sugar readings obtained during reactions in our Case 1 are exceedingly high and we think it improbable that the hypoglycemic complex

could have developed with such high levels. On the other hand, the levels remained high for at least the two hours of observation, so that steepness of drop of the blood sugar as a factor productive of the clinical symptomatology can also be discarded. As for the possibility of an inadequate supply of sugar to the brain or some disturbance in its utilization by the brain, one can only theorize since at present there are no available data on the sugar content of human brain nor on the precise mechanism of the intermediary carbohydrate metabolism in the central nervous system. Another explanation which could account for such unusual reactions will be offered in the latter part of this presentation.

2. Electro-Cortical Dysfunction. Of the seven patients with labile diabetes, only one had a normal initial electroencephalogram. The abnormalities recorded in the remaining six patients can be grouped as follows: Low to moderate voltage fast activity was noted in three cases (among them Case 3); occasional sharp formations and spike potentials in two cases (among them Case 1); irregularities in wave contours in one case (Case 3); and slow 2 to 3 cycle per second activity in one case (Case 1). Hyperventilation did not alter the electroencephalographic pattern in four cases, and in others resulted in a few high voltage 5 to 8 cps potentials. These electroencephalograms were interpreted as borderline tracings in three patients, as consistent with convulsive tendency in two patients (among them Case 3) and suggestive of an epileptogenic focus in Case 1 (figure 1).

As mentioned earlier, to avoid a possible effect of low blood glucose concentrations on the electroencephalographic pattern the recordings were made after a normal meal and only at a time when the patients exhibited no subjective nor objective signs of hypoglycemic reactions.

In a study of spontaneous hypoglycemia in association with electrocerebral dysfunction [1] the electroencephalographic abnormalities were found not to be correlated with the blood sugar variations and it was concluded that the disturbed cortical activity did not represent a cerebral reaction to low blood sugar concentrations. Similarly, in the group of labile diabetics herein presented, deviations from the normal electroencephalographic pattern occurred in absence of low blood sugar levels and in consequence cannot be ascribed to the effect of the injected insulin. This is particularly well demonstrated by Case 1. On anticonvulsive therapy this patient was able to step up the dosage of insulin appreciably. He obtained better control of his diabetes, his blood sugar was reduced to normal levels, and yet reactions which were so frequent before anticonvulsive therapy was instituted disappeared almost completely.

Another question that may be raised is whether the reactions were not related to the diabetic condition per se. Greenblatt et al.[23] have recently reported on the occurrence of electroencephalographic abnormalities in diabetics with severe insulin reactions. The writers do not seem to consider the abnormal brain waves as secondary manifestations of repeated insulin reactions or of the diabetic state as such. Of great significance in this con-

nection may also be the fact that we were able to record disordered electroencephalographic patterns in several non-diabetic blood relatives of our patients. Thus a disturbed brain wave test was obtained in a sister of Case 2 as well as in a sister of another patient and two daughters of still another patient with labile diabetes and electrocortical dysfunction; but in contrast to the patients with labile diabetes, their relatives were suffering from spontaneous hypoglycemia. Since electroencephalographic abnormalities may occur in members of the same family with such opposed disturbances of the carbohydrate metabolism as diabetes and spontaneous hypoglycemia, it ensues that the abnormal cortical potentials cannot be correlated with diabetes as such. It is conceivable that they may be rather genetic in origin, but of course our observations are too scanty to justify any conclusion to this effect. Another point of importance is the improvement noted in control electroencephalograms obtained in patients 1 and 3 after prolonged administration of anticonvulsants (figures 1 and 2). This fact too may be taken to mean that the disturbance of cerebral electroactivity originally recorded in these patients was not produced by their diabetic condition as such.

3. Nature of Reactions. Hypoglycemic and Pseudohypoglycemic Reactions. Being aware that a number of their distressing symptoms are known to be usually associated with low blood sugar values, our patients have ascribed all their reactions to an overdose of insulin and have applied the common measures to combat insulin reactions. These, however, in a large proportion of reactions proved ineffective, and blood sugar determinations made in the course of such refractory reactions gave surprisingly high readings.

It becomes necessary then to consider what constitutes a hypoglycemic reaction. To a clinician, a reaction is thought of in terms of clinical symptoms which are assumed to result from abnormally low blood sugar levels or, in their absence from an abrupt fall of the blood sugar. Our observations, however, indicate that two types of reactions may exist in labile diabetes, one which is produced by hypoglycemia and responds to carbohydrate administration, and another which may develop even with high blood sugar values and is uninfluenced by carbohydrate therapy. Since the latter may be completely controlled by anticonvulsive therapy, it may be assumed that it is brought about by a disturbance of cerebral function which is independent of the concentration of sugar carried by the blood to the brain. Greenblatt et al. in their above quoted work have expressed the opinion that severe reactions in labile diabetes are due to both the unstable carbohydrate regulation and the unstable cortical function. They have thus called attention to the possibility that the distortion of the normal electroencephalographic pattern may be significant in the production of insulin reactions, but they failed to determine the exact position of abnormal brain waves in the mechanism of reactions in labile diabetes. Our studies, by separating the two varieties of reactions, form the basis for a dual theory

of reactions. According to this concept one group of reactions is produced by cerebral glycopenia, i.e., by disturbances in supply of glucose to or its utilization by the brain; the other group by disturbances in cerebral function which may arise with a normal or even an overabundant supply of glucose to the brain. It may therefore be suggested that the term of hypoglycemic or insulin reactions be reserved for reactions which are actually produced by hypoglycemic blood sugar concentrations, and the term of pseudohypoglycemic reactions be applied to those which develop in absence of actual hypoglycemia. The differentiation between the two varieties of reactions cannot be made on the clinical basis, but their delineation can be made easily with the aid of laboratory data, namely, the blood sugar determinations during attacks and the electroencephalographic study of the patient. The differentiation can also be supported by the therapeutic use of anticonvulsants.

The distinction between the two varieties of reactions appears to be of considerable practical importance. Since clinical manifestations in both types of reactions are indistinguishable, a pseudohypoglycemic reaction may be improperly taken for an insulin reaction and treated as such. The intake of large amounts of carbohydrates, although ineffective in warding off such a reaction, must unavoidably increase the magnitude of hyperglycemia and glycosuria and thus aggravate the diabetic condition. On the other hand, correction of the electrocerebral dysfunction may greatly facilitate the management and improve the outlook and the course of the disease.

Another point of importance is that the disturbed cortical function may intensify an actual insulin reaction or modify its character. Thus before the use of anticonvulsants, reactions in patients 1 and 3 were extremely sudden in onset and showed marked resistance to carbohydrate therapy, whereas on anticonvulsant therapy there were premonitory symptoms, the reactions grew slowly and their intensity was decreased.

4. Dosage and Effect of Anticonvulsant Therapy. Three drugs were used in an attempt to influence the cerebral dysfunction, namely, tridione, dilantin and mesantoin.

Tridione was administered to two patients (Cases 1 and 3) but because there was immediately a significant increase in the rate and severity of reactions and because of distressing side effects, the drug had to be discontinued after five to eight days of trial. Since tridione is known to aggravate epileptic symptoms temporarily, it appears possible that in our cases with a more prolonged administration the results ultimately would have been more satisfactory. Further study to determine the usefulness of tridione in labile diabetes seems indicated.

Very favorable results were obtained with dilantin which was administered to all three patients, as well as with mesantoin which was used in two patients. The drugs were given for periods of 10 days with rest periods of five to seven days. For the sake of observation, on some occasions the administration of dilantin was continued for up to 55 days and long control

periods were interposed. During the initial period of treatment the patients responded within 24 hours after the first dose, but later when the drug was readministered after control periods, three or four days were usually required to obtain relief. The improvement was maintained as long as the drug was given and continued on the average up to five days after cessation of therapy. Temporary discontinuation of administration produced no side effects and caused no aggravation beyond that observed before the therapy was inaugurated.

The daily dose of dilantin and mesantoin depended upon the evidence of clinical improvement. On the whole dilantin was given at the rate of 3 to 5 capsules a day and mesantoin in doses of 2 to 3 tablets daily. No undesirable side effects were noted except for bleeding from gums in Case 1 while on dilantin, but this could be controlled with oral administration of vitamin K so that the treatment did not have to be discontinued.

The response to the two anticonvulsants was excellent in two cases (Cases 1 and 2) and less favorable but definite in the third case. The results obtained can be summed up as follows:

(*A*) *Effect on Reactions.* The drugs have reduced the rate of reactions remarkably. In Case 2 the total number of days with reactions in a six month period prior to the use of dilantin was 48, while on dilantin it dropped to 25. Under this therapy the patient repeatedly remained without an attack for a period of over three weeks, which is the longest free period from the onset of her diabetes. There was an almost complete disappearance of reactions in Case 1 both on dilantin and mesantoin, and in Case 3 in which only dilantin was used. Of great significance is also the complete freedom from reactions at night in Cases 1 and 2.

Although with the aid of anticonvulsants the blood sugar values were reduced to a more physiological range the intensity of reactions was also favorably influenced. Patient 1, for instance, had no recurrences of severe and moderately severe attacks and experienced mild symptoms only at mealtime. Patient 2 was free from attacks on arising although her morning specimens for weeks were sugar free.

Lastly, the onset of reactions which was precipitous before the drugs were administered became smoothed out and gradual so that patients had time to apply proper measures before the reactions could grow deep. This was particularly appreciated by patients 1 and 2.

(*B*) *Effect on Hyperglycemia and Glycosuria.* As a result of the improvement in the rate and intensity of reactions the use of additional excessively high carbohydrate feedings was eliminated and in consequence hyperglycemia with glycosuria which usually followed reactions was prevented. Also, since the patients were able to adhere to their basic diets, the excretion of sugar was reduced and it was less subject to rapid variations. Remarkable, too, was the subsidence of premenstrual glycosuria in Case 3.

(*C*) *Effect on Insulin Requirement.* Because of severe reactions which in labile diabetes may follow the administration of even small amounts of

insulin, high blood sugar concentrations and glycosuria cannot be prevented and as suggested by Wilder, in such patients "aglycosuric urine should be carefully avoided." [13] Anticonvulsants proved very valuable in overcoming this difficulty. With their aid we were able, in the initial period of treatment, to step up the dosage of insulin safely and without the risk of reactions. As soon as the blood sugar level was lowered, the number of days with spilling sugar markedly reduced and the need for additional amounts of insulin to cope with unexplained bouts of glycosuria eliminated, it became possible to carry out the program of decreasing the insulin dosage. This is best illustrated by Cases 1 and 2 where after a preliminary increase in insulin we were able to effect an appreciable reduction in the basic requirement of insulin.

(*D*) *Effect on Behavior Disorders.* The personality disorders in labile diabetes may be related to the unstable character of this condition and the inherent difficulties in its management as well as to the distortion of the electrocerebral activity in some of such patients. These patients are anxious to keep sugar free but dread the incapacitating reactions. If they remain sugar free through the continuous and of necessity excessive use of insulin, they develop a state of constant hypoglycemic anxiety which is often mistaken for psychoneurosis, hysteria, etc. If, on the other hand, glycosuria cannot be avoided, they live in fear of diabetic complications and are apt to develop a feeling of guilt. Suspected by their physicians of breaking the diet and lack of honesty or stigmatized as neurotics or hypochondriacs they feel humiliated and lose faith in the medical profession. Humiliation, feeling of guilt and helplessness are indeed frequent accompaniments of labile diabetes.

In those in whom electroencephalographic abnormalities are present, the cerebral dysrhythmia may possibly contribute or predispose the individual to behavior disorders. Of interest in this connection might be the recently reported beneficial results obtained with anticonvulsant medications in problem children with electroencephalographic abnormalities.[24]

Under anticonvulsive therapy all three patients studied showed a remarkable psychologic improvement. As soon as the incidence and intensity of reactions were reduced, the fear of reactions abated. Subsidence of heavy glycosuria, on the other hand, has relieved the patients from fear of diabetic complications. With stabilization of diabetes, the anxiety, nervous tension and irritability were alleviated, the ability to concentrate and to work increased and as a corollary the patients exhibited a general feeling of well-being. A rather startling effect was obtained in Case 3. The severe premenstrual depression coinciding with large excretion of sugar which this patient experienced for years and which was unresponsive to insulin therapy was successfully influenced by anticonvulsive medication.

It is of interest to note that although some of the patients may have had personality disorders not related to their diabetes or to alterations of the

electroencephalogram, psychotherapy of itself which was applied in Case 3 was of no appreciable value to the patient.

Conclusions

1. A group of seven labile diabetics with no family history of epilepsy, and no clinical evidence of epilepsy, was studied. A normal electroencephalogram was obtained in one patient and abnormal or borderline tracings in the other six. Of the latter, three were treated with anticonvulsants for a period of 13 to 17 months.

2. The electroencephalographic abnormalities recorded in this group of patients were shown not to be due to the effect of administered insulin, and they were assumed not to be related to the diabetic condition per se. A possibility of a genetic or constitutional factor responsible for these electroencephalographic alterations was suggested.

3. It was shown that reactions usually associated with insulin hypoglycemia may occur in labile diabetes at the time of exceedingly high blood sugar readings. Such reactions were found to be refractory to carbohydrate therapy, but were favorably influenced by anticonvulsive therapy.

4. A dual theory of reactions in labile diabetes associated with electrocerebral dysfunction was proposed. According to this concept, reactions were separated into two varieties, namely, virtual hypoglycemic reactions which respond to carbohydrate therapy and pseudohypoglycemic reactions which occur with normo- or hyperglycemic values and remain uninfluenced by carbohydrate administration.

5. Two anticonvulsants, namely, dilantin and mesantoin proved highly effective in the management of the patients studied. With improvement of diabetes under this therapy there was also a remarkable psychologic improvement. A return of the EEG to normal in the course of treatment was noted in two patients. Toxic reactions with the two anticonvulsants used were practically absent.

6. The importance of electroencephalographic studies in labile diabetes was pointed out. The recognition of cerebral dysfunction in this type of diabetes may aid in differentiating the two types of reactions and in consequence it may be translated into therapeutic terms.

7. Although the number of patients suffering from labile diabetes in whom anticonvulsants were studied has been small, and observations have extended for a little more than a year, the percentage and the magnitude of satisfactory results were appreciable. These results suggest the use of anticonvulsants as an additional and very valuable therapeutic measure in the management of labile diabetes.

Note: Since this paper was submitted for publication another of this group of patients was given mesantoin for a period of 10 months. Subjective and objective improvement was noted even though the insulin dosage was markedly increased. On the other hand, no effect was obtained in the only patient of this group who had a normal EEG. He was given mesantoin on the assumption that he may have a disturbance in electrocortical activity not reflected in the EEG. He took the drug for six weeks.

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CONDITIONS TO BE DIFFERENTIATED IN THE ROENTGEN DIAGNOSIS OF PULMONARY TUBERCULOSIS *

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THE use of roentgenology as an aid in the diagnosis of chest disease is now standard medical practice. Conservative physicians, be they internists, radiologists or chest specialists, are well aware of the fact that the bacteriological origin of the disease which produces a shadow in the roentgenogram cannot be determined from the roentgenogram alone. This important fact is sometimes lost sight of, especially by enthusiastic proponents of mass chest roentgen-ray surveys.

In order that physicians may have a convenient reference list of diseases, disorders and anomalies which may resemble pulmonary tuberculosis in the roentgenogram, that is, which may cast shadows identical with those cast by pulmonary tuberculosis in its various forms, this short article is being presented.

It is realized that some of the conditions listed are quite uncommon. Nevertheless, when millions of persons are being examined radiologically every year, occasional instances of these rarer lesions will arise, and their elucidation will be aided if the patient does not start off with an incorrect diagnosis of tuberculosis and then has to be reorientated to the correct diagnosis.

The use of properly performed skin tests, sputum examinations, gastric washes and cultures is too well known to need description here. The fact that hemoptysis is more common in bronchiectasis than in pulmonary tuberculosis is fairly well appreciated. But the fact that, as in all laboratory tests, an occasional false positive roentgenogram may be obtained is not sufficiently known by clinicians and public.

The author has seen examples of all of the conditions listed during some 21 years of radiological practice, and has seen them confused with pulmonary tuberculosis or miscalled pulmonary tuberculosis, with the exception of the four entities followed by a minus sign in parentheses. Authenticated cases are available, in the literature, in which these four also were the source of erroneous roentgen diagnoses of tuberculosis.

Diseases, Disorders and Anomalies Which May Resemble Pulmonary Tuberculosis in the Roentgenogram

A. Anatomic Variations

1. Broad vascular markings
2. Anomalous fissures and veins
3. Sternocleidomastoid tendon

* Presented, by invitation, before the annual meeting of the American College of Physicians, San Francisco, April 19–23, 1948.

4. Rib cartilage calcifications
5. Rib anomalies
6. Muscle, etc. folds (e.g. following mastectomy)
7. Bronchial and vascular anomalies
8. Bronchial cartilage calcifications

B. Shadows of Extrinsic Origin Including Artefacts

9. Coils of hair over lung apex
10. Clothing
11. Medication on skin
12. Cutaneous lesions (warts, etc.)
13. Subcutaneous nodules (fibromata, foreign material, etc.)
14. Tumors of the thoracic wall
15. Enlarged or calcified nodes (lower neck, axillae, etc.)
16. Screen defects
17. Processing defects (especially undeveloped areas)
18. Rib irregularities (excess callus, surgery, etc.)

C. Diseases of Lymphatics

19. Adenopathy, non specific (hilar, etc.)
20. Lymphangitis, non specific
21. Hodgkin's disease
22. Lymphosarcoma
23. Leukemia
24. Carcinoma, metastatic (lymphatic spread)
25. Sarcoidosis (Boeck)
26. Silicosis
27. Silicatosis, etc.?

D. Diseases and Disorders of Blood Vessels

28. Venous dilatation (passive congestion)
29. Arterial dilatation (especially congenital cardiovascular lesions)
30. Arteriosclerosis (pulmonary arteries)
31. Infarcts
32. Visceral angiitis (periarteritis nodosum)
33. Edema, lobar
34. Edema, lobular
35. Arteriovenous fistula
36. Pulmonary phleboliths (—)

E. Bronchial Disorders

37. Bronchial filling (blood, fluid, etc.)
38. Bronchial stenosis, mechanical (extrinsic)
39. Bronchial stenosis (inflammatory)
40. Bronchial stenosis, neoplastic (benign)
41. Bronchial stenosis, neoplastic (malignant)
42. Bronchial occlusion, intrinsic (foreign body, mucus plug, etc.)
43. Bronchiectasis
44. Cystic disease
45. Disc atelectasis

F. Parenchymal Lesions Inflammatory (Infiltration or Consolidation)

46. Bronchopneumonia
47. Lobar pneumonia (especially developing or resolving)
48. Pneumonitis unclassified
49. Pneumonia, aspiration
50. Viral pneumonia
51. Eosinophilic "pneumonia" (pulmonary hives, L. H. G.)
52. Lipid pneumonitis
53. Coccidioidomycosis
54. Actinomycosis
55. Blastomycosis (—)
56. Streptothricosis
57. Histoplasmosis

58. Bagassosis (—)
59. Silicosis with infection
60. Asbestosis with infection
61. Paragonimiasis (endemic hemoptysis)
62. Unclassified tropical diseases
63. Miscellaneous unclassified infections (e.g. lupus erythematosus)

Neoplastic

64. Carcinoma primary
65. Carcinoma metastatic
66. Sarcoma primary
67. Sarcoma metastatic
68. Lymphoblastoma (infiltr.)
69. Benign tumor

Miscellaneous

70. Cystic disease
71. Fibrosis (e.g. post-radiation)
72. Calcification
73. Cavitation (e.g. silicotic, etc.)
74. Emphysema (esp. apical bullae, etc.)
75. Compression (e.g. paramediastinal, etc.)
76. Alveolar lipiodol residues
77. Intrapulmonary hemorrhage
78. Siderosis
79. Unclassified occupational disorders (beryllium, etc.)
80. Allergic disorders (?)
81. Eosinophilic granuloma (—)

G. Pleural Lesions

82. Edema
83. Effusion
84. Thickening
85. Calcification
86. Tumor

H. Miscellaneous

87. Polycythemia vera
88. Crushing injuries
89. "Blast" lung

Summary

A reference list of diseases, disorders and anomalies which may resemble pulmonary tuberculosis in the roentgenogram is presented.

PROTEIN BALANCE STUDIES IN PATIENTS WITH LIVER DAMAGE. II. THE RÔLE OF LIPOTROPIC AGENTS *

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DURING the decade 1932–1942 a considerable body of data accumulated, which completely revamped prior concepts of liver damage, in that nutritional factors assumed a rôle of increasing importance in pathogenesis, prophylaxis, and treatment. The experimental work which produced this revolution emanated from several groups of investigators.

Best, Hershey and Huntsman [1] in 1932 showed that choline would prevent fatty liver, and in 1935 Best and Huntsman [2] noted that casein acted in a similar fashion when administered to rats on a high fat diet. In 1937 Tucker and Eckstein [3] demonstrated that methionine was largely, if not entirely, responsible for the "lipotropic" (i.e., hepatic-fat-mobilizing) effect of casein.

In 1939 György and Goldblatt [4] reported the occurrence of hepatic necrosis in rats on "vitamin 'B' " deficient diets. Griffith and Wade,[5] the same year, found fatty livers and hemorrhagic kidneys in animals maintained on low choline diets, and suggested that the relative cystine-methionine content of the diet might modify the choline requirement.

This entire picture was brought into focus in 1941 by reports from four groups of investigators, working independently, that "cirrhosis" (necrosis) could be induced by a low protein, high fat diet, and that such necrosis could be decreased in severity or prevented by the addition of choline, betaine, methionine, or higher levels of casein. The investigators responsible were György, McCollum, Sebrell, Webster, and their respective coworkers.[6, 7, 8, 9, 10]

It was also noted by some of these investigators that cystine aggravated the damage produced by a low choline and/or low methionine intake.

Protection against liver damage referable to carbon tetrachloride,[11] yellow fever virus,[12] and ethylene dichloride [13] in experimental animals has been conferred by the administration of excess amounts of choline. Similar observations have been made in the case of methionine [14, 15, 16, 17, 18] although only in protein depleted animals.

* This paper was presented in part at the annual meeting of the Western Society for Clinical Research, which met in San Francisco on November 8, 1947. Received for publication March 18, 1948.

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Acknowledgments are made to Dr. Cox, of the Mead-Johnson Company, for supplies of Amigen; to the Wyeth Company, for supplies of methionine, "Meonine"; to Anheuser-Busch, Inc., for supplies of yeast of high vitamin content; to the Eli Lilly Company, for supplies of alpha tocopherol.

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The above observations, together with a large body of related investigation in other laboratories, performed during this same period, raised a host of questions, foremost among which were:

1. What might be the relationship between the types of experimental liver injury described above, to clinical human liver damage, acute and chronic?

2. Through what channels did methionine and choline exert their protective effects; why did cystine at least under some circumstances, aggravate the experimental liver damage?

3. Would methionine and/or choline prove to have specific therapeutic value in clinical liver damage, over and above the therapeutic effectiveness of a high protein diet as originally advocated by Patek [19, 20] and amplified by Connor? [21]

The final answer to the identity between experimental nutritional deficiency liver injury and human "hepatitis" and "cirrhosis" is still to come. It is discussed elsewhere.[22] Certainly there is much evidence in favor of such identity or at least of marked similarity in the respective pathological pictures.

As to the channels through which methionine and choline produce their protective effects, there is agreement on only one point, and speculation and disagreement beyond that point. Essentially complete agreement exists in regard to the mechanism of the lipotropic effects of choline and methionine. Choline itself is an essential constituent of phospholipids. Phospholipids are apparently essential for the normal transport of fat from the liver to fat depots. Inadequacy of available choline, therefore, results in an increasing amount of liver fat, as originally demonstrated by Best and his coworkers [1, 23, 24, 25] and since that time confirmed and added to by many investigators. Methionine, in turn, can serve as a choline precursor by virtue of its labile methyl groups, as demonstrated by du Vigneaud [26] in 1941. Ethanolamine (derived from glycine) was shown by Stetten [27] in 1942 to serve as a nonmethylated precursor of choline. The steps in this formation are shown in figure 1.

Considerable disagreement and confusion exist beyond this point, chiefly in regard to:

1. The rôle of other amino acids and "vitamins," fatty acids, inositol, lipocaic, etc.—much too extensive a subject to discuss here.

2. The question as to whether methionine, perhaps by virtue of its sulfur content, plays some specific protective rôle not related to its function as a methyl donator. This will be further discussed in this paper. The observations of Tucker and Eckstein [3] and of György and Goldblatt, previously noted,[6, 10] are in point.

The evaluation of methionine and/or choline in the treatment of acute and chronic liver disease in the human is the specific function of this report. Data already in the literature are not too conclusive, chiefly because of the lack of controlled objective criteria.

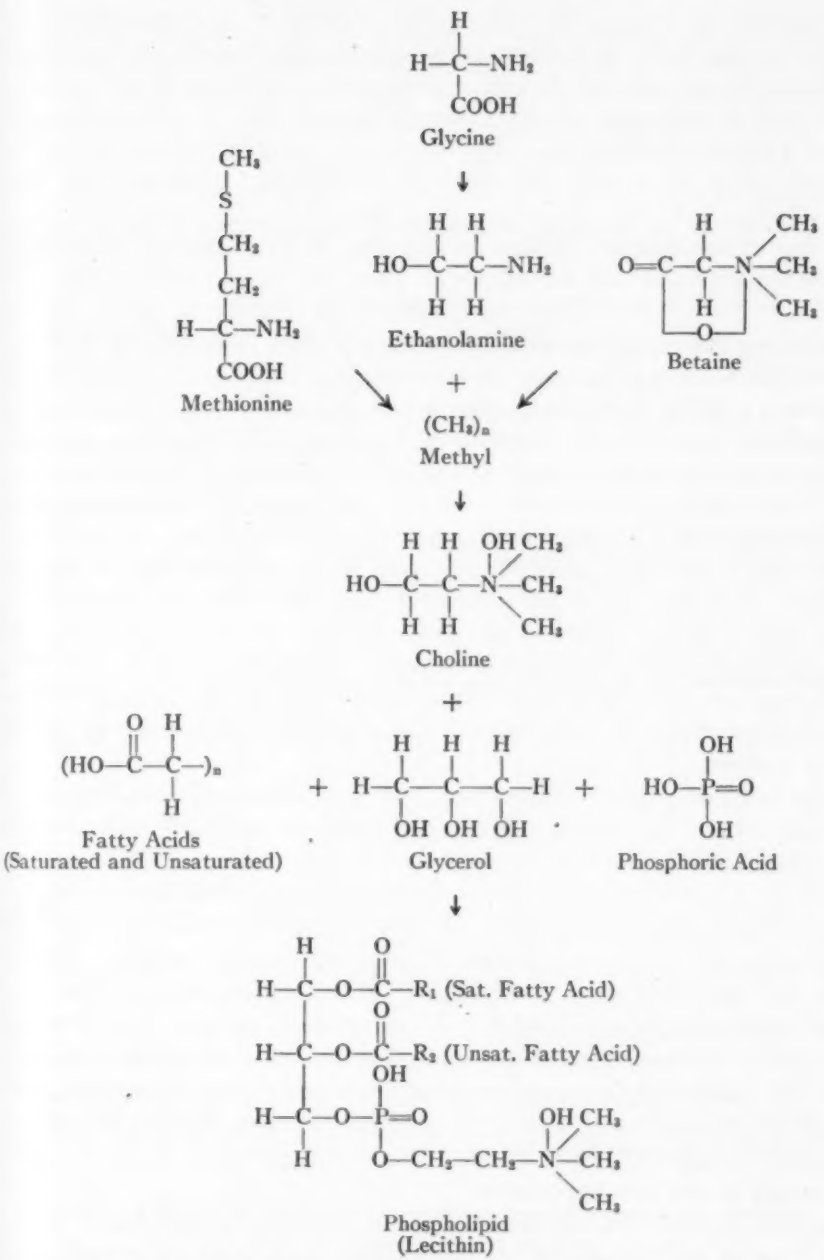

FIG. 1. Phospholipid formation. The rôle of choline and methionine.

Broun and Muether,[28, 29] Russakoff and Blumberg,[30] Beams,[31] and Morrison [32] have reported series of patients with chronic liver damage treated with choline and/or methionine, with or without a high protein intake, and are fairly unanimous in their belief that these agents are of some value.

Beattie and co-workers,[33, 34] Marshall,[35] Peters, et al.[36] and Eddy[37, 38] report the prophylactic and therapeutic use of methionine in individuals exposed to carbon tetrachloride and arsenic, and conclude that the evidence is in favor of a protective effect. Stewart and O'Brien[39] take issue with Professor Beattie's conclusions. Hartmann and Singer[40] report a case of arsenic poisoning in which they felt that methionine administration was without effect.

The use of methionine, choline and cystine in the treatment of patients with acute hepatitis has been the subject of a considerable body of reports.[41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53] The interpretation of results is varied but in most instances the data interpreted are insufficiently controlled. This is, of course, the weakness inherent in most clinical evaluation unless the effectiveness of a given therapeutic agent is unequivocal. The extreme degree of spontaneous variation in intensity and duration of infectious hepatitis makes for more than average difficulty in such evaluation. As will be noted presently, this same spontaneous variation has made the interpretation of some of our own data in patients with acute liver disease somewhat difficult.

It seemed to us, then, that the question as to whether choline and/or methionine, *over and above the amount present in a diet containing large amounts of protein and adequate quantities of other dietary constituents has a beneficial effect on patients with liver damage,* still remained to be answered.

It did not seem probable that further evaluation on the basis of clinical observation, or change in usual liver function tests would help to supply the necessary answer.

In the original paper in this series[54] it was postulated that because of insufficiency of normal protein anabolic and catabolic processes, patients with liver disease would tend to be in negative nitrogen balance, this despite the failure of Post and Patek[55] to demonstrate such a negative balance in such patients. Our findings for the most part confirmed those of Patek and Post; i.e., a consistently negative nitrogen balance was rarely found in patients with severe liver damage. Nonetheless, it seemed inescapable that such patients must have major qualitative disturbances in protein formation and if this were so, it seemed not improbable that the administration of methionine and/or choline might correct to some degree this qualitative defect, with the resultant production of a strongly positive nitrogen balance in response to the administration of these agents. The work presently to be discussed was designed to test this hypothesis.

Immediately after the beginning of this work, reports by Johnson et al.[56] and by Cox et al.[57] appeared simultaneously, indicating that methionine added to the diet of humans (without liver damage) did *not* affect the nitrogen balance, in contrast to the positive effects noted in rats and dogs by Allison, Anderson and Seeley[58] and by Brush, Willman and Swanson.[59] To the best of our knowledge, no similar human data are available in regard to choline.

In view of the greater protective effect of methionine as compared to choline in experimental animals as previously noted [5, 6, 10] and also as shown by Miller and Whipple in dogs,[60] we anticipated that if any effect were demonstrable methionine would have a greater effect than choline.

The work which follows presents the data accumulated in four patients with chronic liver damage ("cirrhosis"), one with "idiopathic hypoproteinemia," six with acute hepatitis, one with chronic hepatitis, and one with a mild hemolytic jaundice.

Methods

The diets employed, the procedures followed in patients studied during intravenous feeding, the analytical methods used are all presented in the first paper in this series.[54] Specific details will be described in the presentation of data on individual patients.

The balance charts follow the rules shown in the following diagram (figure 2).

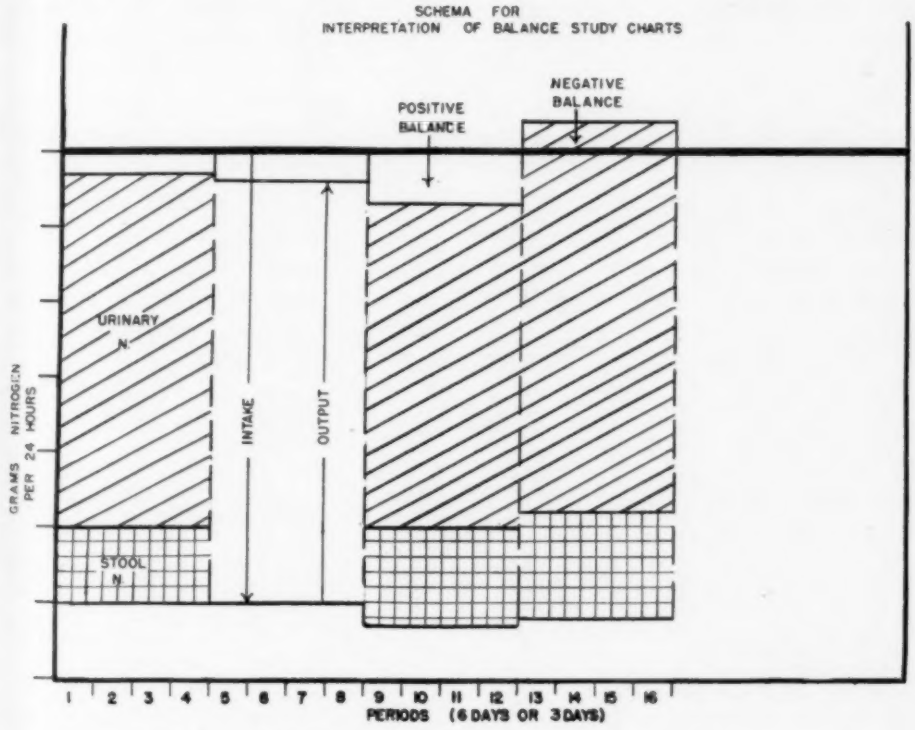

Fig. 2. Schema for interpretation of the balance charts.

Findings

Chronic Liver Damage:

Two Long Term Oral Balance Studies. The two men presented in this category both had a history of chronic alcoholism of more than 20 years'

duration; both were in the fourth decade; each had ascites on admission, which in the case of patient DAN had responded to dietary therapy prior to the beginning of this study; and which never responded to any therapy in patient DRE. The clinical, biopsy and liver function data on these men are presented in detail elsewhere.[22] Suffice it to say here that all liver function tests performed, including the A/G ratios, bromsulfalein-excretion, cephalin-flocculation, glycogen storage index, thymol turbidity, and serum bilirubin, were abnormal before, during, and after the balance study, and that clinically and histologically the findings in these men were in every sense of the word compatible with a diagnosis of advanced, active, chronic liver damage, referable to longstanding alcoholism, coupled with recurrent dietary insufficiency.

Both men were placed on the same balance diet, a three-day rotating, high protein, high vitamin (including supplemental vitamin K), high carbohydrate, moderately low fat, iso-caloric intake, as previously described, and had identical regimes up to the seventy-second day of the study, at which time patient DAN, because of domestic worries, became uncoöperative, with resultant undependability of his findings. Patient DRE continued for 96 days as originally planned.

All therapeutic periods were 12 days in length. Except for liver extract and alpha tocopherol, all medications and dietary supplements, once started, were continued throughout the entire period of study; i.e., the program was cumulative, up to the final 12-day post-treatment period (in DRE), at which time all medication was discontinued.

It will be noted that we purposefully used a diet which by any standard could be considered as thoroughly adequate, so that if any effect were obtained with any supplement, it could be considered as a specific effect.

The supplements added (figures 3 and 4) were in order:

Yeast, dried brewers' (Anheuser-Busch)—60 grams daily.
Choline chloride (by mouth)—9 grams daily.
Liver extract, crude (Eli Lilly & Company)—1 c.c. daily, I.M.
DL-methionine (Meonine, Wyeth, Inc.)—8 grams daily, by mouth, as 0.5 gram compressed tablets.
Alpha tocopherol (Eli Lilly & Co.)—300 mg. orally and then intramuscularly.

Effects of Supplements in Patient DAN, Age 44 (figures 3 and 3a):

Yeast

Reason for giving: Because of its high vitamin, high protein content.

Effects: Increased stool nitrogen. Decreased over-all nitrogen retention, with the production of a slightly negative as compared to a previously slightly positive balance. Clinical effects: none observable.

Evaluation: No significant effect.

Choline

Reason for giving: For its "lipotropic" effect.

Effects: A marked decrease in excretion of urinary nitrogen, with the production of a strongly positive nitrogen balance—equivalent to

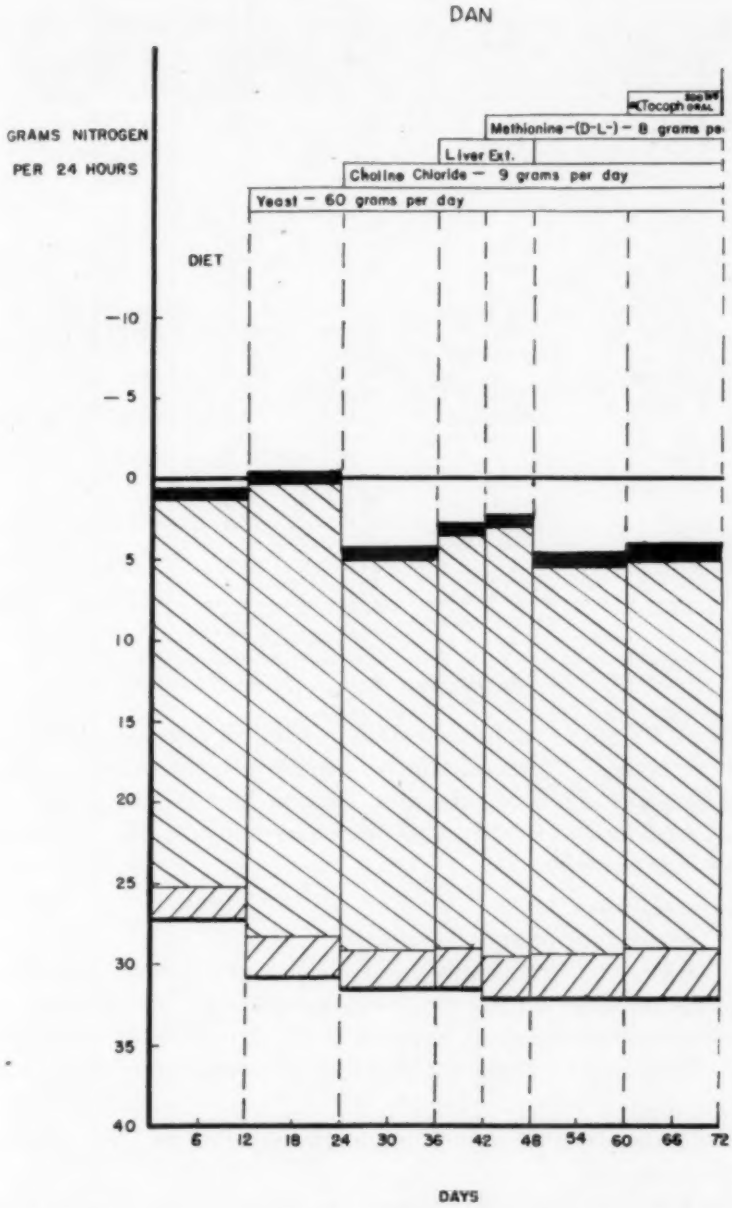

FIG. 3. Chronic liver damage. Effect of dietary supplements upon the nitrogen balance, patient DAN.

DAN

Date	Period	Treatment (All medications cumulative except liver extract)	Daily			Balance
			Nitrogen Intake	Stool Nitrogen	Urine Nitrogen	
4/3/47	1	Diet	27.2	2.5	19.9	+ .40
4/6/47			27.2	2.5	28.3	
4/9/47			27.2	2.2	26.0	
4/12/47			27.2	2.2	23.0	
4/15/47	2	Plus yeast	30.9	2.8	27.6	− .37
4/18/47			30.9	2.8	26.0	
4/21/47			30.9	2.5	29.5	
4/24/47			30.9	2.5	31.6	
4/27/47	3	Plus choline	31.7	2.5	24.4	+4.52
4/30/47			31.7	2.5	25.6	
5/3/47			31.7	2.5	23.6	
5/6/47			31.7	2.5	25.1	
5/9/47	3a	Plus liver extract	31.7	2.5	26.9	+3.00
5/12/47			31.7	2.5	25.5	
5/15/47	3b	Plus methionine	32.0	2.8	26.6	+2.30
5/18/47			32.0	2.8	27.3	
5/21/47	4	Stopped liver extract	32.0	2.5	25.6	+4.60
5/24/47			32.0	2.5	27.6	
5/27/47			32.0	3.0	22.6	
5/30/47			32.0	3.0	22.8	
6/2/47	5	Alpha tocopherol 300 mg. oral	32.0	2.8	26.0	+4.05
6/5/57			32.0	2.8	23.1	
6/8/47			32.0	3.3	27.3	
6/11/47			32.0	3.3	23.2	

FIG. 3a. Balance data on patient DAN.

about 30 grams of protein daily. Clinical effects: clinical improvement noted. Chemical effects: hepatic glycogen storage became less abnormal. Prothrombin time became less abnormal.

Evaluation: Protein anabolic effect unequivocal. Apparent clinical improvement.

Liver Extract

Reason for giving: Empirical.

Effects: Decreasingly positive nitrogen balance, which reverted to its previous level when liver extract was discontinued. Clinical effects—none noted, as compared to patient DRE (vide infra).

Evaluation: Unfavorable effect in terms of nitrogen balance.

Methionine

Reason for giving: For its lipotropic effect, and sulfur content (vide supra).

Effects: Nitrogen balance: no significantly greater effect than that already produced by choline. Clinical effects: continuing improvement.

Evaluation: No unequivocal evidence of any effect over and above that already initiated by choline.

Alpha Tocopherol (to be discussed elsewhere).

Effects of Supplements in Patient DRE, Age 49 (figures 4 and 4a):

It is to be emphasized that throughout the entire period of study, this man was constantly accumulating ascitic fluid. This presumably accounts for his positive balance, despite the progressive loss of body musculature which characterized him clinically, and which was only slightly retarded by the later administration of 100 gm. of serum albumin daily.

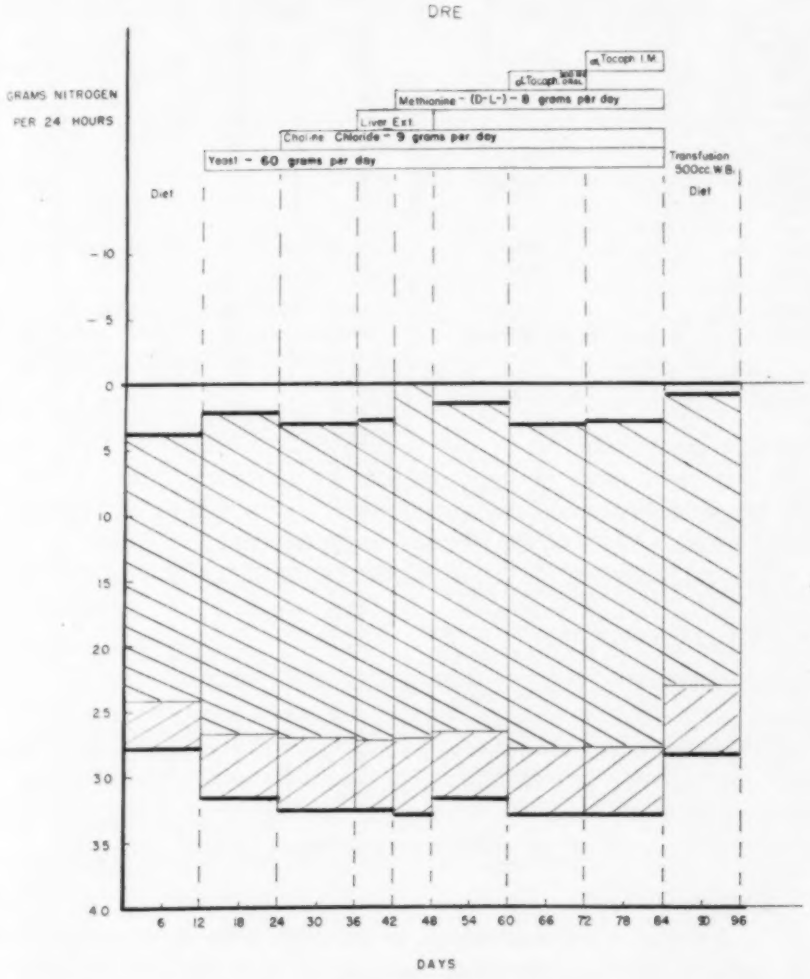

FIG. 4. Chronic liver damage. Effect of dietary supplements upon the nitrogen balance, patient DRE.

Yeast

Effects and evaluation as in DAN, only of greater magnitude. The stool nitrogen increased very markedly (32 per cent).

DRE

Date	Period	Treatment (All medications cumulative except liver extract)	Daily			Balance
			Nitrogen Intake	Stool Nitrogen	Urine Nitrogen	
4/3/47	1	Diet ammonium chloride	28.0	4.3	20.5	+4.20
4/6/47			28.0	4.3	19.5	
4/9/47			28.0	3.3	19.5	
4/12/47			28.0	3.3	20.5	
4/15/47	2	Plus yeast	31.7	4.5	24.1	+2.10
4/18/47			31.7	4.5	24.0	
4/21/47			31.7	5.5	24.3	
4/24/47			31.7	5.5	26.5	
4/27/47	3	Plus choline	32.5	5.8	22.8	+2.92
4/30/47			32.5	5.8	24.3	
5/3/47			32.5	5.5	24.6	
5/6/47			32.5	5.5	24.0	
5/9/47	3a	Plus liver extract	32.5	5.5	25.1	+2.55
5/12/47			32.5	5.5	23.8	
5/15/47	3b	Plus methionine	32.8	5.8	28.0	− .20
5/18/47			32.8	5.8	26.3	
5/21/47	4	Liver extract stopped	28.5	5.2	23.3	+1.67
5/24/47			32.8	5.2	26.3	
5/27/47			32.8	5.2	25.0	
5/30/47			32.8	5.2	24.8	
6/2/47	5	Plus alpha tocopherol, 300 mg. oral	32.8	5.3	24.7	+3.12
6/5/47			32.8	5.3	25.2	
6/8/47			32.8	4.8	24.4	
6/11/47			32.8	4.8	24.2	
6/14/47	6	Stopped alpha tocopherol. Began intramuscular alpha tocoph.	32.8	5.2	24.3	+2.64
6/17/47			32.8	5.2	25.5	
6/20/47			32.8	5.3	25.3	
6/23/47			32.8	5.3	24.6	
	7	Whole blood				
6/26/47		Diet ammonium chloride	26.6	5.3	21.4	+1.47
6/29 47			26.6	5.2	21.2	
7/2/47			33.6	5.3	21.7	
7/5/47			26.6	5.3	22.2	

FIG. 4a. Balance data on patient DRE.

Choline

Effects: No improvement in nitrogen balance over that noted in control period, presumably because of quantitative and qualitative insufficiency of liver tissue, i.e., inability to respond to stimulation.

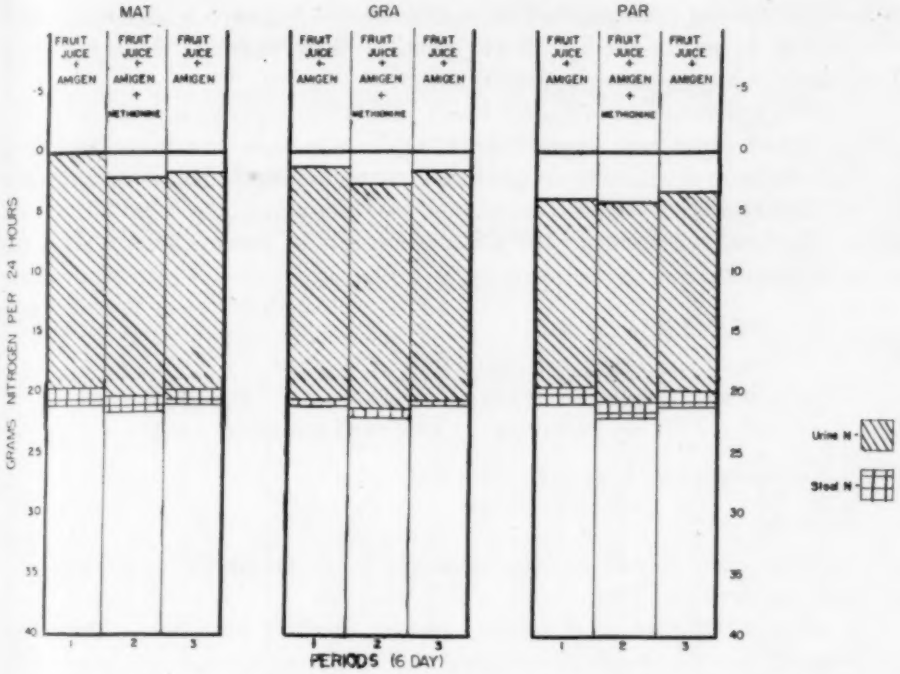

FIG. 5. Short term intravenous protein balance studies. Methionine effect. Patient MAT—idiopathic hypoproteinemia; patient GRA—chronic liver disease, active; patient PAR—chronic liver disease, active, convalescent.

Liver Extract

Effects: Fluid retention appeared to be accelerated during this period; this increased retention disappeared when liver was discontinued. The nitrogen balance became progressively less positive.

Evaluation: Apparent unfavorable clinical and chemical effects. It was discontinued in both men because of the fluid retention in this patient.

Methionine

Effects: Nitrogen balance essentially identical with that observed during the control period, i.e., no evidence of any effect. Except for possible slight decrease in the rate of formation of ascites, no clinical or chemical improvement was noted throughout the study.

CHRONIC LIVER DAMAGE ET AL.:

Three Short Term Intravenous Studies (figure 5):

Description of Patients:

MAT, aged 40 (Described in detail elsewhere).

Diagnosis: Idiopathic hypoproteinemia, without demonstrable liver damage.

Clinical and Laboratory Findings at Time of Study: Anasarca, ascites, extreme hypoproteinemia, liver function tests normal, liver histology normal, moderate anemia, malnutrition.

Diet (identical for all three men): 3000 c.c. 5 per cent protein hydrolysate and 5 per cent glucose daily, by intravenous infusion. Sufficient fruit juice and vitamin supplements to make diet adequate calorically and dietetically.

Methionine: 9 gm. of the DL material daily, intravenously, as 3 per cent solution.

Balance Study:

Pre-methionine (6 days): Just in balance.
On methionine (6 days): Retention of 2.5 gm. daily.
Off methionine (6 days): Continued retention.

Interpretation: Positive methionine effect.

GRA, age 48;

Diagnosis: Chronic liver damage, with an acute exacerbation—ethanol-dietary origin.

Clinical Status at Time of Study: Clinical jaundice—decreasing. Palpable liver. Steady clinical and chemical improvement prior to study. No ascites.

Balance Study:

Pre-methionine (6 days): Retention of 1.3 gm./d.
On methionine (6 days): Retention of 2.9 gm./d.
Off methionine (6 days): Retention of 1.7 gm./d.

Interpretation: Significant methionine effect.

PAR, age 49:

Diagnosis: Chronic liver damage, active, regenerative—ethanol-dietary origin.

Clinical Status at Time of Study: Liver down 3 to 4 cm.; no jaundice; increasing energy; liver function tests becoming progressively less abnormal. Ascites had disappeared 3 to 4 months before this study.

Balance Study:

Pre-methionine (6 days): Strongly positive balance.
On methionine: Essentially unchanged.
Off methionine: Essentially unchanged.

Interpretation: Patient in strongly regenerative phase of chronic liver disease, not significantly influenced by extra-dietary methionine.

Both patients GRA and PAR had had large amounts of methionine by mouth up to two weeks before this study was performed. This may

have some bearing on the relative slightness of intravenous methionine effect on the nitrogen balance.

ACUTE AND SUBACUTE HEPATITIS; HEMOLYTIC SYNDROME:

Eight patients have been studied, six with acute viral hepatitis of varying severity; one with chronic hepatitis of fairly severe degree, and one with a low grade hemolytic jaundice (the latter for comparative purposes). The rapidly changing course of the disease, and the consequent shortness of the metabolic periods, makes the entire procedure less than desirable from the standpoint of interpretation.

All of these studies have been "intravenous" studies, the technics being

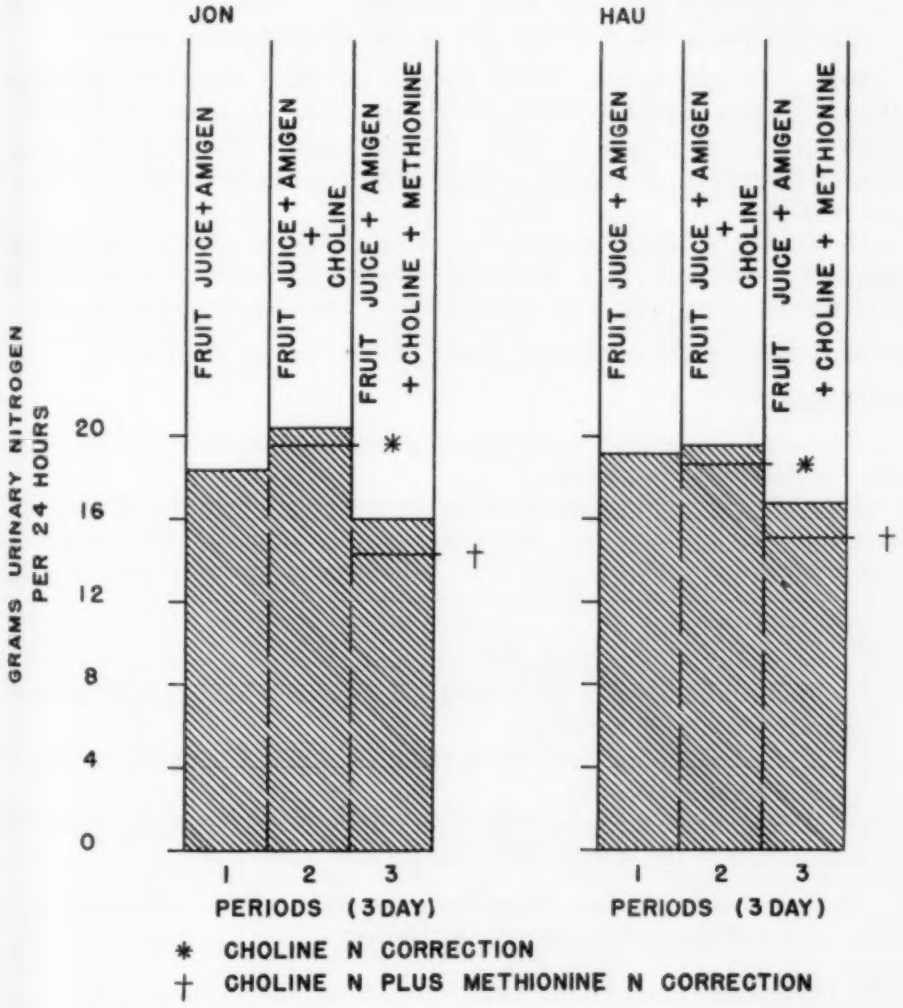

FIG. 6. Short term balance study in two patients with acute hepatitis.

essentially identical with those used in the preceding three patients, except that choline and methionine have been given by mouth instead of by vein.

Patients JON and HAU, aged 24 and 32, respectively (figure 6):

Diagnosis: Hepatitis, acute, severe. Duration 4 and 7 weeks respectively.

Clinical Status at Time of Beginning Study: Both patients were still severely jaundiced, with all liver function tests abnormal. Serum albumin—normal. Serum globulin—increased. During the nine days on the study, their liver function tests became progressively less abnormal.

Balance Study: Stool nitrogens were not done. Hence, only the urinary output is graphed. The intake was constant throughout, except for the added choline and methionine, and was essentially identical with that received by all other patients on the intravenous program.

Both men appeared to obtain no positive effect from choline, but a strongly positive (anabolic) effect from methionine. It would seem unlikely that a decrease in urinary nitrogen output of about 4 grams per day would be referable only to spontaneous clinical improvement, in the short period of time involved.

Evaluation: Probably a significant protein anabolic effect of methionine; apparently no choline effect (the increased nitrogen excretion on choline can be attributed to the increased nitrogen intake referable to choline per se).

Patients BRO, BRU and CAS (figure 7):

BRO, age 19:

Diagnosis: Hepatitis, acute, moderate severity; secondary lues. Duration (of jaundice), two weeks.

Clinical Status: Findings, those of classical acute hepatitis of somewhat more than average severity. All of the usual liver function tests were moderately abnormal. Progressive, slow improvement during period of study.

Balance Study:

Diet Only (3 days): Negative balance.

Diet Plus Choline (3 days): Strongly positive balance (net gain of 5 grams of nitrogen per day).

Diet Plus Choline Plus Methionine (3 days): Continued but not increased positive balance.

Methionine Stopped (3 days): Positive balance of same magnitude maintained in the second and third periods noted above.

Interpretation: Choline: significant anabolic effect. Methionine: no effect over and above that produced by choline.

BRU, age 21:

Diagnosis: Hemolytic state, of mild degree; idiopathic albuminuria.

Clinical Findings: Jaundice, mild, intermittently present for many years. Albuminuria without other evidence of renal damage. Red cell fragility—increased at times. Fecal urobilinogen—not increased. Liver function tests: slightly abnormal at times. Liver histology (biopsy): normal. Nutrition: excellent. Symptoms: none.

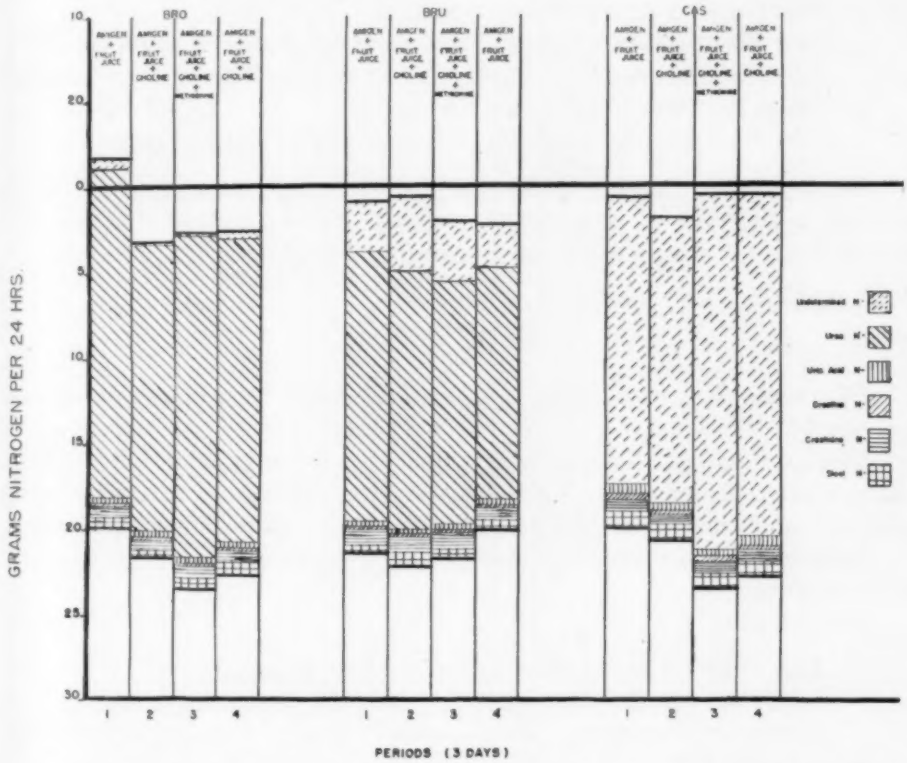

FIG. 7. Short term intravenous nitrogen balance studies. BRO—hepatitis, acute; BRU—jaundice, hemolytic, mild; CAS—hepatitis, acute. In patient CAS, urea was not determined, as such; i.e., "Undetermined N" in this patient *includes* urea N. The significance of the nitrogen partition is discussed elsewhere.[54] The large amount of "undetermined N" in BRU, at least in part, is referable to albuminuria. Dosage: Choline chloride, 9 gm. per day (oral); methionine (DL), 8 gm. per day (oral).

Balance Study:

Diet Only (3 days): Positive balance.

Diet Plus Choline (3 days): No effect.

Diet Plus Choline Plus Methionine (3 days): Strongly positive balance (net gain of about 2 grams daily).

Diet Only (3 days): Identical with the third period.

Interpretation: No choline effect; anabolic effect from methionine, maintained for some days after methionine was stopped.

CAS, age 24:

Diagnosis: Hepatitis, acute, moderately severe.

Clinical Findings: Essentially identical with patient BRO. Clinical improvement during study.

Balance Study:

Diet Only (3 days): Positive balance.

Diet Plus Choline (3 days): Net gain of 2 grams of nitrogen daily.

Diet Plus Choline Plus Methionine (3 days): Reversion to same excretion as that noted during the first period.

Diet Plus Choline (3 days): Identical with the third period.

Interpretation: None—unless one postulates that some limiting factor, perhaps a shortage of some other essential dietary constituent, operates, preventing more than a given amount of protein storage.

Patients CUM, REY and WIL (figure 8):

CUM, age 27:

Diagnosis: Hepatitis, chronic. Onset of acute hepatitis seven months previously.

Clinical Findings: Nutrition, fair; spider angiomata, many; liver enlargement, 4 cm.; splenomegaly, slight; hepatic fetor, definite; liver function tests, majority abnormal; liver histology, fibrosis and hepatocellular abnormality.

Subsequent Progress: Continuing evidence of an active, subacute hepatotoxic process.

Balance Study:

Diet Only (3 days): Strongly positive protein balance.

Diet Plus Choline (3 days): Significantly less positive balance.

Diet Plus Choline Plus Methionine (3 days): Balance identical with second period.

Diet Plus Choline (3 days): Slightly more positive balance.

Interpretation: In doubt. This man clinically fails to make an adequate response to any and all of the usually effective therapeutic agents. The paradoxical decrease in nitrogen retention with choline and methionine may be referable to the same obscure factors.

REY, age 25:

Diagnosis: Hepatitis, acute, moderate. Duration of 2½ weeks.

Clinical Findings: Typical for the disease. Decreasingly abnormal function tests during period of study.

Balance Study:

Diet Only (3 days): Strongly positive balance.

Diet Plus Choline (3 days): Identical with first period.

Diet Plus Choline Plus Methionine: Less positive balance.
Diet Plus Choline: Slightly less positive balance than in third period.

Interpretation: None. The concept of a lack of some other material, essential to protein anabolism might explain such observations.

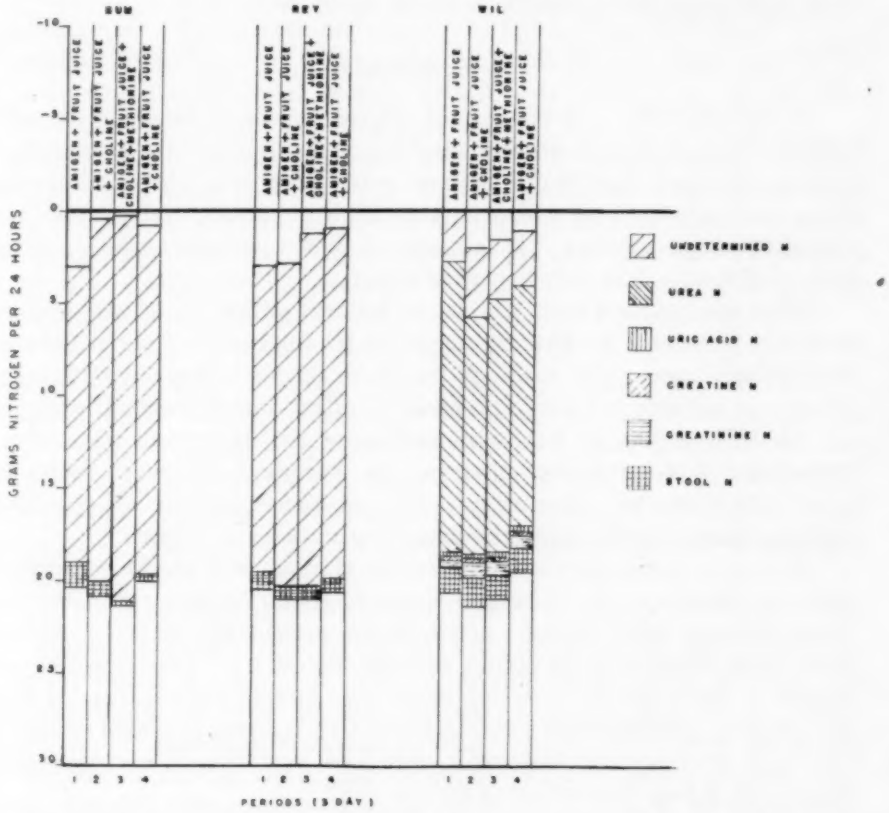

FIG. 8. Short term intravenous nitrogen balance studies. Patient CUM—chronic hepatitis, active; patient REY—hepatitis, acute, moderate; patient WIL—hepatitis, convalescent. Nitrogen partition data presented elsewhere. "Undetermined N" in CUM and REY includes *all* urinary N—i.e., partition not done. Dosage: Choline chloride, 9 gm. per day (oral); methionine (DL), 8 gm. per day (oral).

WIL, age 34:

Diagnosis: Hepatitis, convalescent. Onset 6 weeks previously.
Clinical Findings: No icterus remaining, slight hepatomegaly, symptom free. Most liver function tests still slightly positive.

Balance Study:

Diet Only (3 days): Just in balance.
Diet Plus Choline (3 days): Strongly positive balance.

Diet Plus Choline Plus Methionine (3 days): Less positive balance by about 1 gram of nitrogen daily.

Diet Only (3 days): Still less positive.

Interpretation: Anabolic effect of choline with a "wearing out effect" which is in no way inhibited by methionine. The hypothesis of the need for some additional, indispensable nutrient again arises.

Discussion

As stated earlier, the purpose of this work was to establish the effect or lack of effect of choline and/or methionine in terms of the production of a positive nitrogen balance, in patients with acute and chronic liver disease when these agents were added to diets high in protein and vitamin content, and adequate in calories. It is assumed that a protein anabolic effect may be regarded as a definitely beneficial effect.

Since the question had been raised but not settled, as to whether methionine acts only as a choline precursor in its relation to liver pathology, we purposefully have constructed all but three of our balance studies in such a manner as to bring out any "non-choline" effect of methionine if such existed.

We believe that we have obtained some satisfactory answers, and some stimulating but perplexing observations, the mechanisms of which at the present time are less than clear. The substance of these observations and interpretations, drawn from the preceding data, is as follows:

(1) *In chronic, active liver disease* choline will produce a profoundly positive effect upon the nitrogen balance, assuming that the dietary intake is adequate in other respects and that the patient has sufficient salvageable liver tissue remaining to permit of such effects.* † This effect is perhaps related to some effect of choline other than simple mobilization of liver fat, inasmuch as patient DAN, whose data, of all patients included in this study, are most unequivocal, had no histological evidence of excess hepatic fat deposition during the period of this study.[22]

(2) *In chronic, active liver disease* we have no data which would suggest that methionine augments the protein anabolic effect of choline.

(3) *In chronic, active liver disease* methionine will apparently augment the protein anabolic processes initiated by an adequate diet, the protein of which is derived entirely from intravenous casein enzymatic hydrolysate (figure 5). That the effect was not more dramatic in these men, may be attributable to previous intensive methionine administration.

(4) *Patients with extreme protein depletion of non-hepatic origin* may

*Since the completion of this study, patient DRE has died from progressive hepatic insufficiency, despite literally quarts of serum albumin; thus substantiating the concept of inability to respond positively to choline or any other stimulus in a manner identical with his running mate, DAN, because of previous extensive and irreversible liver damage.

† Further studies since the completion of this manuscript indicate that choline can produce an impressive anabolic effect in patients who have failed to manifest any anabolic response to methionine. It has also been shown that methionine in large dosage can be toxic to some individuals with severe liver damage.

obtain an anabolic effect from methionine (MAT, figure 5). This apparent contradiction to the findings of other workers [56, 57] may be referable to the *cause* of the protein depletion. Further study in this matter is progressing at the present time.

(5) In the evaluation of *patients with acute liver damage* (figures 6, 7, and 8) we feel on much less secure ground, chiefly because of the rapidly changing nature of the disease under study, itself a potentially major factor in the production of nitrogen balance changes; plus the attendant impossibility of obtaining experimental periods (control or treatment) of sufficient length to make unequivocal any data obtained.

Of the six acute hepatitis patients presented, three apparently obtained an anabolic effect from choline, three showed no effect. Two appeared to receive a positive effect from methionine as opposed to choline; one received no additional effect from methionine, as compared to choline alone, and three were actually in less positive balance with the addition of methionine than with choline alone, not an impressive array of data, all things considered.

(6) *One man with chronic, active hepatitis* (CUM, figure 8) appeared to receive an actual catabolic effect from choline and methionine—conceivably this observation as well as some similar observations on the acute patients might be explained by the same type of hypothesis as that devised to explain the "antilipotropic" effects of cysteine. Certainly this catabolic effect of a normally anabolic agent is no harder to explain than the failure of this man and many others like him to make a satisfactory clinical response to adequate rest, diet, and dietary supplements.

(7) Critical evaluation of the other dietary supplements—yeast, liver extract, alpha tocopherol—used in the course of the long term balance studies must await further work. It is perhaps permissible to speculate as to the significance of the increased urinary nitrogen in patients DAN and DRE (figures 3 and 4) during liver extract administration. But for the increased fluid retention in patient DRE, the increased nitrogen would probably not have been noted in time to stop the liver extract after a single 12 day period.

The late Dr. Hoagland and his coworkers have waxed rather enthusiastic over the beneficial effects of liver extract in cirrhotics [61] although their enthusiasm has been considerably tempered and diluted by time. It is not impossible that the beneficial effects which they observed may have been largely or entirely attributable to a high protein, high vitamin intake.

The observations of McHenry and Gavin [62, 63] regarding "biotin liver injury" may have some bearing on our findings. In any event, it may be well to put liver extract in the category of a possibly harmful agent in patients with liver damage, until further data are available.

(8) The probable significance of the huge amount of stool nitrogen in patient DRE together with a consideration of fluid balance changes and of the indications for different forms and avenues of administration of protein, are discussed in the first paper in this series.[54]

Summary

1. Choline and/or methionine over and above a high protein, high vitamin intake, have a protein anabolic effect in patients with chronic liver damage. This is probably another way of saying that they are potent therapeutic agents in some of these patients.

2. The effectiveness of these agents in patients with acute hepatitis is less clear cut. The intrinsic variability of the disease makes evaluation difficult, even under the controlled conditions of a balance study.

3. Our data do not establish any greater effect of methionine than of choline upon the protein balance. Since all patients received a high protein diet, it may be that the "choline effect" was actually a methionine sparing effect. The lack of fat in the biopsy sections would indicate some effect other than mere lipotropism.

4. Certain short term observations are reported in regard to the use of liver extract in patients with severe liver damage, which raise the question of deleterious rather than beneficial effects of this material.

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A NEW TREATMENT FOR THE RELIEF OF OBLITERATIVE DISEASES OF PERIPHERAL ARTERIES *

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Introduction

Complete success in treating chronic obliterative peripheral arterial diseases depends upon stopping the progression of the pathological process and then developing a collateral circulation which will compensate for the arterial insufficiency. In thromboangiitis obliterans when smoking is stopped at least a recession of the superficial phlebitis can be expected, in a relatively short time. No specific measures are available in the management of arteriosclerosis. There are currently available many modes of therapy which have been devised with the hope of developing a competent collateral circulation. When improvement does follow their use it has taken so long that it is difficult not to credit time alone for the improvement. When vasodilator drugs are given intravenously or subcutaneously they usually fail in the lower extremities. The one exception is sympathectomy which, because of its immediate effect, has received wide acceptance. Its applicability, however, is limited in the arteriosclerotic group by the increased surgical risk commonly presented by older patients with cardiovascular arteriosclerosis and other degenerative diseases. That its immediate benefit will persist long enough to meet the future problems presented by a progression of the pathological process is questionable. It is apparent that a sympathectomy cannot be repeated several times if new indications arise. Grimson, in his review on the limitations of sympathectomy as a lasting measure, says that its immediate benefits fade with time due to the regeneration of the nerves and the sensitization of the muscles of the arteries.[2]

A procedure which can reproduce the immediate benefits of a sympathectomy and be repeated if new developments make it necessary, should be a most useful means of treating the obliterative peripheral arterial diseases. On the basis of recent preliminary studies in which radioactive sodium was utilized as a measure of changes in circulation it was found that the intra-arterial infusion of a dilute solution of histamine could approach this ideal.[3] We are now reporting its use in the femoral artery in patients with a severe insufficiency of the peripheral arterial circulation of their lower extremities caused by an endarteritis obliterans due to thromboangiitis or arteriosclerosis.

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Method

Technic of Histamine Infusion. To overcome the pressure in the femoral artery the infusion bottle was prepared in the following manner. It was necessary to introduce the solution at a higher pressure than the diastolic pressure in the artery. The ordinary 500 c.c. infusion burette was capped by a stopper with two holes which was held down tightly with several strips of adhesive tape. Through one opening in the stopper, a piece of glass tubing was inserted reaching above the histamine solution. The outer end of this tube which contained an air filter was connected to two parts of the ordinary blood pressure apparatus by means of a Y tube. With the arm cuff rolled up snugly and held so with a stout elastic band, its rubber tubing was connected to one arm of the Y tube and the tubing of the manometer to the other. A closed circuit was thus established. When the bulb was inflated positive pressure was created in the inverted infusion bottle. This could be measured by the mercury manometer of the blood pressure apparatus.

With the skin and subcutaneous tissue anesthetized with procaine, a two inch, 20 gauge needle was introduced into the femoral artery.

To date well over 500 arterial punctures have been made and at no time have any local intra- or extraarterial complications resulted. An opportunity to examine the popliteal artery about two weeks after an intraarterial infusion of histamine occurred recently. The pathologist found no evidence of the recent puncture.

The bright red blood and its pulsating thrust into a Kaufman syringe attached to the needle were evidence of entry into the artery. The pressure was then raised or lowered until the pulsating blood could be seen only during each systole of the heart. The solution consisted of 500 c.c. of normal saline to which was added between 1.38 and 2.75 mg. of histamine acid phosphate (Lilly) equivalent respectively to 0.5 mg. and 1.0 mg. of histamine base. The infusion was given weekly and if the symptoms were totally disabling, biweekly. The dropping rate was measured in the drip indicator during the diastolic fall in pressure during which inflow into the artery took place. It was found that between two and five drops per heart beat permitted an erythema of the thigh to develop without any subjective symptoms. An asymptomatic flush of the face was found to be of little importance.

Measurements

The temperatures of the skin were determined with a Leeds Northrup potentiometer. The following method was employed. The local differences in the surface temperatures of the skin are noted and then corrected according to the spontaneous changes of the untreated leg. For example if there is a local rise of 1° C. on the treated foot and a drop of 2° C. on the control foot, the final change on the treated side is recorded as plus 3° C. It is time saving and obviates the necessity for temperature controlled rooms.

Oscillometric readings: Maximum amplitude of the pulsations of the

large vessels was recorded by a Boulitte oscillometer. These were made with the leg and patient in a horizontal position.

The diffusion of radiosodium was studied in many patients and these were recorded graphically.[5] Control measurements made before histamine infusions are termed basic curves. Unless otherwise stated when a graph was made to study the effect of a treatment or a procedure, the sodium was given between 10 and 20 minutes after the completion of the treatment. About 100 microcuries of Na_{24} in about 10 c.c. of water were introduced into the median basilic vein and a count of the radioactive emanation was made over the sole of the foot and the calf of the leg by placing these parts in contact with the window of a Geiger counter. It is our feeling when there is an increase in the diffusion rate of the radiosodium that it represents an increase in blood flow and total surface area of the minute vessels due to their dilatation and/or an increase in the permeability of the capillaries.

Results

The immediate objective responses to an intraarterial infusion of histamine are striking. The degree and extent of these reactions are obviously dependent upon the extent of the arterial block and the availability of a collateral circulation. The effects include a change in the color of the skin, its temperature, a distention of the superficial veins and alteration in the rate of diffusion of radioactive sodium. As the solution of histamine begins to enter the femoral artery a definite erythema spreads over the thigh from the groin and buttock to the knee becoming more intense as the treatment continues. The back of the leg, then the front and last, the foot, become pink. The extent of the spread is variable and patterns appear on the extremity in pink and white which suggest the location and degree of block in the larger vessels. The pale areas may become diffused later if the collaterals are dilated by the histamine. It is of interest to note that if the infusion is given too rapidly, thus permitting histamine to escape into the general circulation, erythema is observed to develop in the upper half of the body while the leg becomes only mottled and the foot even cyanotic. However, when the flow is slowed, permitting fixation of the histamine in the leg, then the skin of the leg and foot becomes pink and the rest of the body remains pale. Such an observation is corroborative evidence of the futility of giving vasodilators intravenously. Its generalized dispersal opens the more sensitive and healthy arteries of the upper half of the body first. Their dilatation diverts blood from the arteries of the lower half because total blood volume is essentially fixed in amount. When this occurs it is not only without value but it may actually be dangerous. This undesirable effect of misplaced vasodilatation has been observed after high sympathectomy when vasodilatation in the lower abdomen was so extensive that it diverted blood from the foot and precipitated gangrene. A rise in skin temperature follows the erythema rapidly in the thigh, more slowly in the foot. It is of interest to note

that the presence of erythema does not necessarily mean a rise in skin temperature. Many patients, however, do show a rise of 6° C. and some show none in the toes. A rise in the temperature of the skin over the calf of the leg is most significant. It indicates that blood flow to the calf muscles has been increased to a magnitude where it might be expected to relieve the pains experienced while walking and sleeping. The diffusion of radiosodium made after an infusion is accelerated indicating increased blood flow. This has been noted consistently over the calf muscles but not over the foot. This is to be expected because the block is more severe and collaterals are less numerous in the foot. The superficial veins invariably become distended even though the horizontal position is maintained. The oscillometric readings in the patients studied (table 1) were all very low as expected because none had palpable popliteal pulsations. Their amplitude never increased after single or multiple infusions of histamine. When a patient has a palpable pulse, the amplitude after a single infusion may rise as high

TABLE I

Oscillometric Readings of Leg Treated with Arterial Infusion of Histamine

Patient	Upper Half	Lower Half
P. K.	2.0	1.0
B. D.	1.0	0.5
S. B.	1.0	0.7
L. P.	0.2	0.1
F. C.	1.0	1.0
O. R.	1.0	1.0
I. W.	0.5	0.1
W. K.	0.5	0.1
H. G.	0.5	0.1
R. S.	0.1	0.0
A. S.	0.1	0.0

as 25 per cent. These immediate and variable manifestations of vasodilatation after a single infusion will be later correlated with the cumulative effects of repeated infusions on walking and sleep tolerance reduced by obliterative disease.

No other treatment was used concurrently in the present study. Suggestion as a factor in improvement is ruled out by the fact that each patient had previously been subjected to one or more types of treatment from nine months to five years together with their attendant encouragement.

To evaluate the efficacy of histamine treatment we have chosen as criteria, benefit of two symptoms of arterial insufficiency in the lower extremities. The first is the number of blocks the patient is able to walk before he is forced to stop by pain in the calf of his leg. The second is sleep tolerance which represents the number of hours the patient can lie in bed in a horizontal position before he is awakened by pain in his calf muscles and forced to get out of bed for relief.

We have grouped all of our patients so that the effect of treatment on walking tolerance can be visualized in figure 1. The time interval between

treatments is not recorded but treatments were given weekly until the walking tolerance was increased to 10 blocks. Then one treatment a month was given until a tolerance of 18 to 20 blocks was attained when treatment ceased. If a recession occurred therapy was resumed until the desired level was again

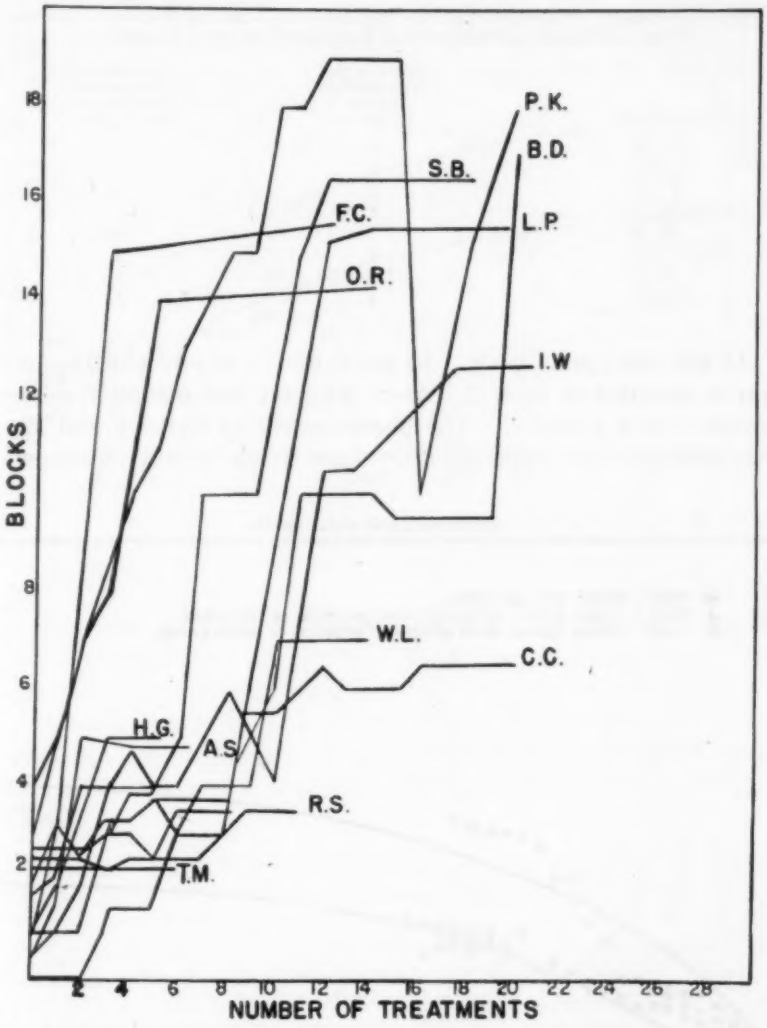

FIG. 1. The effect of repeated infusions of histamine into the femoral artery on decreased walking tolerance in obliterative peripheral arterial disease.

reached. Patients whose response to treatment was of this character were placed in the "very good" group. The response was considered to be only "good" when walking tolerance increased to between six and 10 blocks and reached a plateau. When this stage was reached the interval between treatments was also lengthened without permitting a relapse. The response was

called "poor" when no or negligible improvement was noted after six treatments. The effects on walking tolerance developed in response to histamine therapy as shown in figure 1, were as follows: "very good," 51 per cent;

TABLE II

The Effect of Repeated Infusions of Histamine into the Femoral Artery on Decreased Sleep Tolerance in Obliterative Peripheral Arterial Disease

Patient	Hours in Bed Without Pain Before Treatment	Number of Treatments Needed to Abolish Pain
L. P.	0	5
I. W.	2	2
C. C.	2	2
H. G.	1	4
W. K.	2	5
L. S.	4	3
H. S.	½ hr.	2
P. C.	4	2

"good," 33 per cent; and "poor," 16 per cent. The effect of treatment on sleep pain is recorded in table 2. Here we have had complete success and found patients most grateful. The improvement in walking and sleep tolerance has been prompt appearing after three to six weekly treatments.

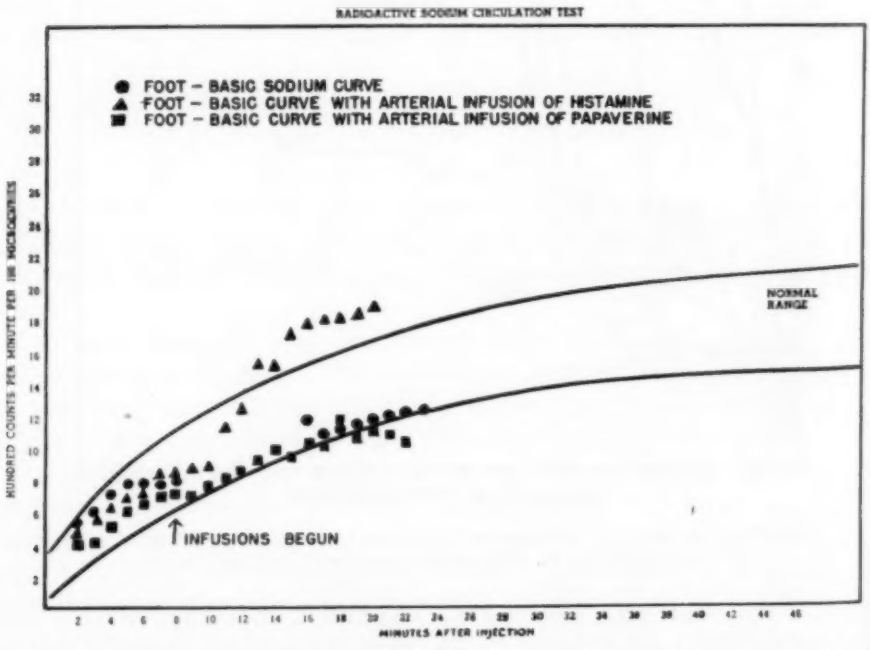

FIG. 2. Three radiosodium diffusion curves, one basic with no infusion, two made while normal saline was given by femoral artery for eight minutes when in one a solution of histamine (histamine base 0.35 mg. in 500 c.c. saline) and in the other a solution of papaverine HCl (90 mg. in 350 c.c. saline) was substituted. Histamine alone increased the Geiger count over the foot of patient I. W.

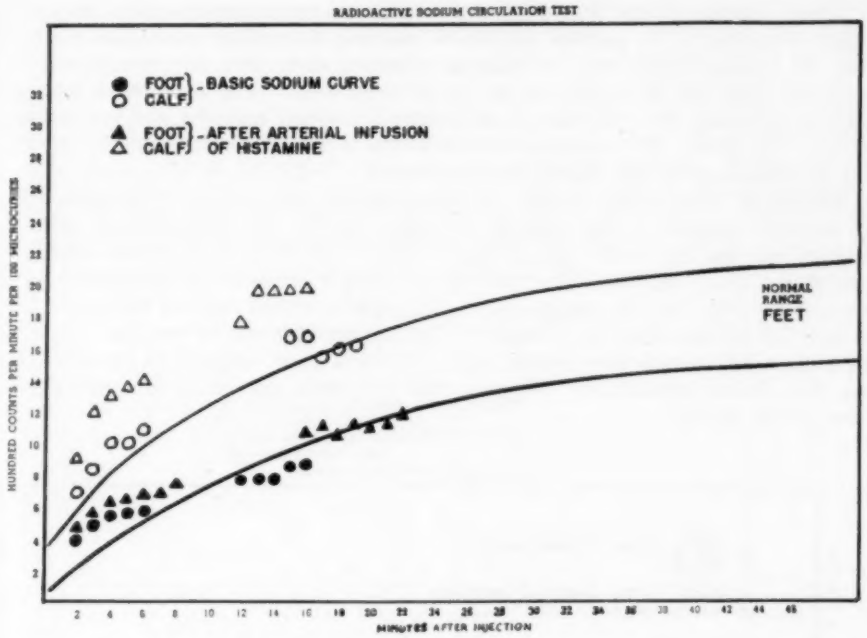

FIG. 3. The effect of an arterial infusion of 500 c.c. normal saline containing 0.5 mg. histamine base on the diffusion of radiosodium given intravenously. An increase in the Geiger count occurred over the calf but not over the foot of patient C. C.

These results produced by multiple infusions of histamine can be correlated with the immediate effects induced by a single infusion. It may establish patterns which could be used in estimating the amount and availability of the collateral circulation and the probability of its responding to this form of treatment. For this purpose a representative case history was chosen for each classification of response to therapy, namely, "very good," "good" and "poor."

Patient I. W. had a "very good" response to therapy. Her walking tolerance rose from one block to 15 blocks in 12 treatments and this improvement was maintained without any treatment for over five months. Before treatment the longest she could stay in bed was two hours and after one treatment her sleep was undisturbed. Her immediate response to a single infusion was just as dramatic (figure 2). The erythema reached down to her toes where the skin temperature rose 6° C. In this patient we found the greatest response in both the immediate and late effects. In contrast some of the patients in this group showed only a fair response to a single infusion. There was no rise in radiosodium diffusion in the foot but a rise in the calf. The increase in skin temperature was only 2° C. and the erythema did not reach the toes.

Patient C. C. exhibited a "good" response to therapy. After an infusion the erythema spread from the groin, down the back of his leg with an occasional blotch of pink on its anterior surface, while the foot remained white. Skin temperature rose on the back of the leg 3° C. and 1° C. on the dorsum of his foot and toes. The diffusion curve of radiosodium rose over the calf muscles but remained unchanged over

the plantar surface of his foot (figure 3). His objective response was not as good as that of patient I. W. and his subjective response to weekly treatments was not as good. It consisted of a rise in walking tolerance from one to seven blocks in 18 treatments and loss of sleep pain in three treatments. The foot, even though he continued working in a cold shed as an automobile repair man, became less numb and warmer. However, his walking tolerance has never risen higher and treatment must be continued to maintain this improvement.

Patient R. S. as representative of "poor" results received six treatments without any marked increase in his walking tolerance and it was discontinued. However, his pain was not as severe and he was able to return to work after having been disabled for many months. He reacted to a single infusion by developing an erythema of his thigh and leg but no rise in the surface temperature of his foot. In fact his first toe became slightly cyanotic. The radiosodium curve rose in his calf and foot (figure 4) and this was perhaps a portent for a good response to therapy. However, this did not materialize. He also had the lowest oscillometric readings of the entire group treated.

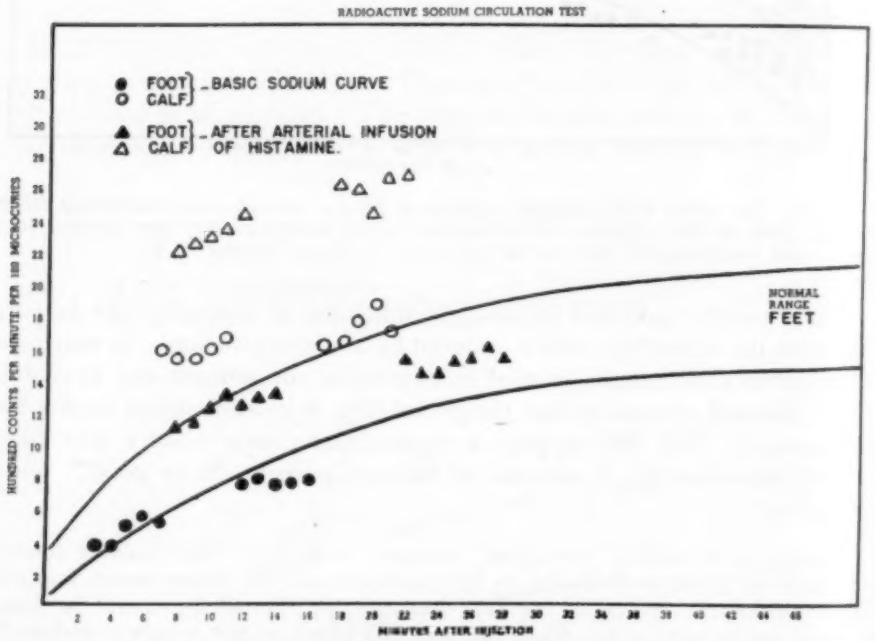

FIG. 4. The effect of an arterial infusion of 500 c.c. normal saline containing 0.5 mg. histamine base on the diffusion of radiosodium given intravenously. An increase in the Geiger count occurred over the foot and calf of patient R. S.

Two cases are recorded to further illustrate the difficulties in establishing the prognosis of therapy, when untoward extravascular events intervene to change the fate of an extremity.

Patient H. S. presented himself in the clinic with a walking tolerance of two blocks; a sleep tolerance of half an hour due to pain in the foot. Two lumbar blocks with procaine were performed but with no relief. They caused no rise in skin temperature and no distention of the veins. Two histamine infusions were then given a

week apart. These induced an erythema down to his toes but no rise in temperature, the superficial veins of the leg dilated, the radiosodium curve in the calf rose but remained unchanged in the foot. There was great clinical improvement, the patient was able to sleep and returned to work. A week later a man stepped on his toes while riding in a crowded subway train. The skin was broken and oozed. All his previous disability returned. Histamine infusions were again given but this time without lasting relief. Sympathetic blocks again gave no help. A bilateral sympathectomy of L_2 and L_3 was performed also without relief. A radiosodium diffusion curve three days after the first sympathectomy was lower than the basic curve made two weeks previously. Trauma, by causing an irrevocable vasospasm, introduced a new load on an already harassed collateral circulation.

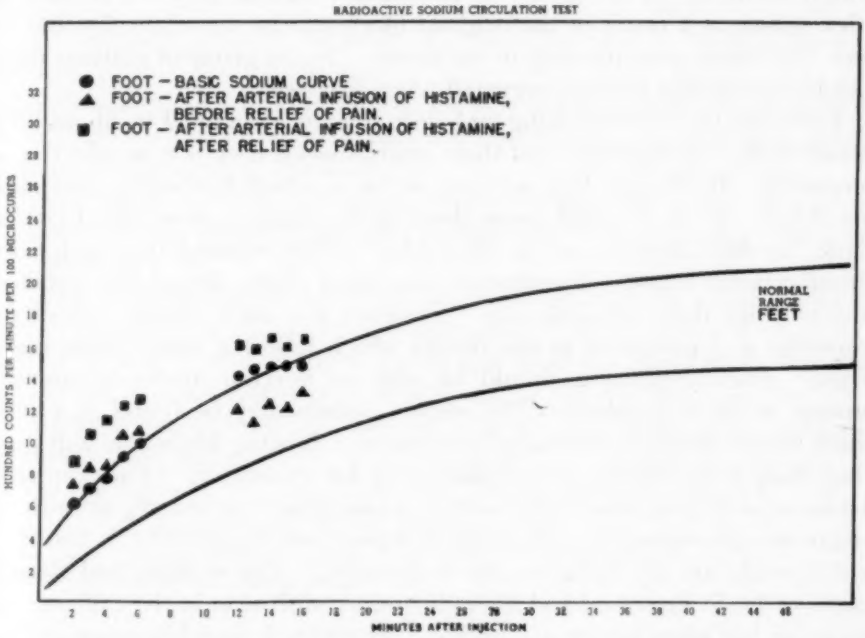

FIG. 5. Before pain due to an ingrown toe nail was relieved, an infusion of histamine induced a fall in radiosodium diffusion over the foot while after the relief of this pain the histamine infusion caused an increase in diffusion.

This is again illustrated by patient T. M. who was referred because of pain in his foot, limited walking tolerance and sleepless nights. Two infusions of histamine failed to cause a rise in radiosodium diffusion over his foot. An ingrown toe nail, partially embedded in the underlying skin, was clipped. The pain in the foot was now relieved. The next infusion of histamine was followed by a moderate rise in radiosodium diffusion. Figure 5 records the effect of pain on the radiosodium diffusion in the foot of this patient.

DISCUSSION

It has been shown that histamine given by arterial infusion is a powerful dilator of all the components of the peripheral vascular system. Its increase of the temperature of the skin and radiosodium diffusion indicates that the arteries, large and small, are widened. The erythema and rubor of the skin

which follow its use mean that the precapillary sphincters are relaxed and the minute vessels are wide open. The superficial veins become visibly dilated. These physiological responses are probably as short lived as six hours, still as the results show cumulative and mounting improvement follows weekly infusion. Therefore it is reasonable to inquire why should such an enduring and competent circulation develop after histamine. An analysis of the problem in full perspective may yield the answer. To begin with, in each patient a primary influence such as smoking or a degenerative process initiates a block in one or more arteries. The arterial collaterals, though available, do not take over the burden because they are thrown into reflex spasm as a result of the original block and its attendant distress. In some, they open spontaneously in six weeks. In the group of patients treated with histamine this had not occurred when first seen.

From the benefit in walking and sleep tolerance obtained by about 85 per cent of them, it is apparent that their arterial blood flow is now effective and competent. In theory there are two ways in which histamine could bring this about. First, it could come about in the manner shown by Clark and Clark [1] in their experiment on the rabbit. They showed that under acute stimuli arterio-venous anastomoses developed from thread-like capillaries to five times their original size. Evidence for such violent vasodilating properties was presented in the results which follow a single histamine infusion. Their repetition should be able to develop arteriovenous anastomoses in great numbers. The second reason may be found in evidence which shows that the reversal of vasospasm following histamine will persist when there is no reflex extravascular cause for vasospasm. Pain can render histamine or a sympathectomy inert as a vasodilator permitting at most only temporary effectiveness. The clinical reports on patients H. S. and T. M. in the results are the basis for this impression. The walking and sleep tolerance of H. S. increased and his radiosodium diffusion in the calf rose after histamine but when his toe was accidentally crushed, then histamine and later a lumbar sympathectomy failed to help him. The latter was followed three days later by a drop in radiosodium diffusion. Similarly T. M. first showed a drop in radiosodium diffusion indicating no vasodilatation following a histamine infusion. After his pain due to an infection and an ingrown toe nail was relieved, the same type of infusion was able to bring about a rise in radiosodium diffusion (figure 5).

Fear has also been shown to be a cause of vasospasm.[4] A recent experience gave visual confirmation of this phenomenon. A marked rubor was developing during an infusion of histamine into the femoral artery of a patient with scleroderma when it suddenly faded completely from her foot after the patient began discussing the details of the death of a close relative. In less than two minutes after the conversation was terminated, with the arterial infusion still running, the pallor was replaced by a bright erythema. Dread fear had again completely reversed the dilatation caused by histamine. It follows then that the crux of the success of histamine therapy rests not

alone on the presence and availability of a collateral circulation which it can activate but also on the absence of a continuing cause for a reflex and histamine resistant vasospasm of these same collaterals. The patterns established in response to a single arterial infusion of histamine are not, as the results show, sharply delineated for each classification of response to therapy. However, when these are correlated with all the variables, vascular and extravascular, it is possible to grade the extent of the occlusion and the probability of circumventing it with histamine given by artery.

Conclusion

1. A new treatment for the relief of obliterative arterial disease has been described.

2. When a dilute solution of histamine is repeatedly given by intraarterial infusion, relief is obtained by the patients who are incapacitated by a limitation in walking and sleep tolerance.

3. Our results show that walking tolerance was raised to normal in about 85 per cent of the patients treated and the pain present during sleep was abolished in all.

4. From the correlation of effects produced by a single intraarterial infusion of histamine on the color and temperature of the skin and the radiosodium diffusion curves of the foot and calf with the final results of treatment, we are decided that it is only by equating the degree of arterial block as shown by these observations with the presence or absence of extravascular causes for spasm that one will be able to prognosticate with some degree of accuracy the outcome and fate of the limb after treatment with histamine.

The author wishes to express his gratitude to Professor Edith H. Quimby and her assistant, Miss Charlotte Schmidt of the Department of Radiological Research, for making the radioactive isotope studies possible.

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CASE REPORTS

THE USE OF TETRAETHYLAMMONIUM BROMIDE AS A DIAGNOSTIC TEST FOR PHEOCHROMOCYTOMA *

By JOHN S. LADUE, M.D., Ph.D., F.A.C.P., PAUL J. MURISON, M.D., and GEORGE T. PACK, M.D., *New York, N. Y.*

INTRODUCTION

THE purpose of this case report is to present and compare the reactions of a patient with a medullary tumor of the adrenal gland (pheochromocytoma) to the intravenous administration of histamine phosphate and of tetraethylammonium bromide.

Roth and Kvale [1] found that three patients with pheochromocytoma who were given 1/40 to 1/20 of a milligram of histamine phosphate intravenously responded with a rise of 100 mm. of Hg or more in the blood pressure reading. Patients who had essential hypertension or hypertension secondary to renal disease and those who were controls or hyper-reactors to the cold pressor test evidenced a slight fall or rise or no change in the blood pressure. Hence, a marked rise in blood pressure after the injection of histamine phosphate has been proposed as a confirmatory test for the presence of a pheochromocytoma.

CASE REPORT

R. S., a 41 year old salesman, had been comparatively well, except for insomnia, nervousness, and bilateral tinnitus of five years' duration, until June, 1945, when he began to have what he called heart attacks. These were characterized by the sudden onset of a nervousness which he described as "a pounding of my heart with the blood rushing to my head," soon followed by sweating, by severe, pounding, generalized headaches, and by terrific abdominal pain, "as if someone had struck me in the solar plexus with his fist." These episodes usually occurred during the day, lasted 10 to 15 minutes, and were not relieved by self-medication, hot packs, or other similar measures. The patient was totally incapacitated during a seizure, being doubled up with pain, unable to suppress moans, and drenched with cold sweat. When the symptoms had subsided he was left completely exhausted for an hour or more. The attacks increased in frequency and severity so that the patient was loath to leave his quarters. Eventually, he noticed that attacks seemed to be precipitated by his lying in bed propped on his left elbow or by a sudden twisting of his body to the left, although his symptoms occasionally appeared while he was lying on his right side. He tired easily and was forced to give up tennis and other strenuous activity. Almost coincidentally with the first of his attacks, he noticed a marked loss of libido.

The patient consulted several physicians and was told that he had high blood pressure. Sedatives were prescribed, and he was advised to avoid nervous tension

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and strenuous exertion. His social background included an unstable childhood environment, an unhappy marriage, and recent unemployment, and this history strengthened the impression that all his complaints might be psychosomatic in origin.

When the patient first presented himself at our offices on July 3, 1946, a little more than a year after his first attack, physical examination revealed a well developed, muscular, well nourished, white male who appeared to be in an excellent state of general health. Except for blood pressure readings varying between 150 and 180 mm. Hg systolic and 100 and 120 mm. diastolic, the physical findings were all within normal limits. Carotid sinus pressure resulted only in a slowing of the heart rate from 90 to 85.

The abdomen was soft and non-tender, and no masses were palpable, although the lower pole of the right kidney was felt. The extremities were symmetrical, and the reflexes were physiological. Mild arteriovenous nicking was noted in the eye grounds.

Routine hematological studies and urine analyses revealed nothing except a trace of albuminuria. The urine concentration test gave a specific gravity of 1.028, and the urea nitrogen was 27.5 mg. per 100 c.c. of blood. Phenolsulfonephthalein excretion was 15 per cent in one-half hour, 25 per cent in one hour, and 5 per cent in the second hour, a total excretion of 30 per cent, on September 11, 1946. By September 16, 1946, the phenolsulfonephthalein excretion had risen to 45 per cent in one-half hour and 60 per cent in one hour, with a total two hour excretion of 60 per cent. The urea nitrogen had fallen to 18.4 mg., and the total protein was 6.10 gm., with 4.30 gm. of albumin and 1.80 gm. of globulin. The blood cholesterol was 441 mg., and the blood sugar 134 mg. per 100 c.c. of blood. Wassermann and Kahn reactions were negative.

An intravenous pyelogram showed that the right kidney was flattened at its superior pole and displaced downward by a soft tissue mass (figure 1). A roentgenogram of the chest was within normal limits; the electrocardiogram showed slight left axis deviation with one millimeter elevation of ST_1 and a one millimeter depression of $ST_{2 \text{ and } 3}$.

On the patient's second office visit, he was asked to try to produce an attack. He succeeded in doing so after five minutes of lying on his left side and raising his shoulder by leaning on his left arm. He then complained of a pounding headache, palpitation, dizziness, and severe epigastric pain. His skin was blanched, and he walked about the room doubled over and moaning with pain. The skin was cold and moist, particularly at the extremities. The pupils were somewhat dilated, and the retinal arterioles could be seen to contract and relax. Respirations were increased (16 to 25) and were somewhat deeper; the heart was regular at 130 beats per minute, and a moderately loud, blowing, apical systolic murmur appeared with an accentuated A_2. The blood pressure rose above 300 mm. Hg systolic (limit of range of the sphygmomanometer) and 160 mm. diastolic, falling to 180 mm. Hg systolic and 150 mm. diastolic within 10 minutes.

A presumptive diagnosis of pheochromocytoma was made, and the patient was admitted to Flower and Fifth Avenue Hospitals on September 8, 1946. The reactions of the patient to the intravenous administration of histamine, tetraethylammonium bromide, and saline were studied preoperatively and are considered in detail later. On September 26, 1946, an 8 by 5 cm. tumor overlying and displacing the superior pole of the right kidney was removed through an oblique right lumbar incision. The pedicle was isolated by blunt dissection and was rapidly ligated, and the encapsulated tumor was removed within four minutes, thus reducing manipulation of the tumor to a minimum.

Since most authors [2, 3, 4] have reported severe shock following removal of these tumors, several precautions were taken. The patient was given spinal anesthesia of nupercaine, using 5 c.c. of a 1:1500 solution, since the specific gravity of this solu-

tion is lighter than that of spinal fluid. This should result in a relatively greater paralysis of the splanchnic nerves on the right than on the left with the patient lying on his left side at operation. Theoretically, this should produce less anesthesia of the splanchnic nerves on the left and should allow them to continue to function after removal of the adrenal tumor on the right. The blood pressure was 180 mm. Hg systolic and 105 mm. diastolic just before handling of the tumor was begun, and it rose

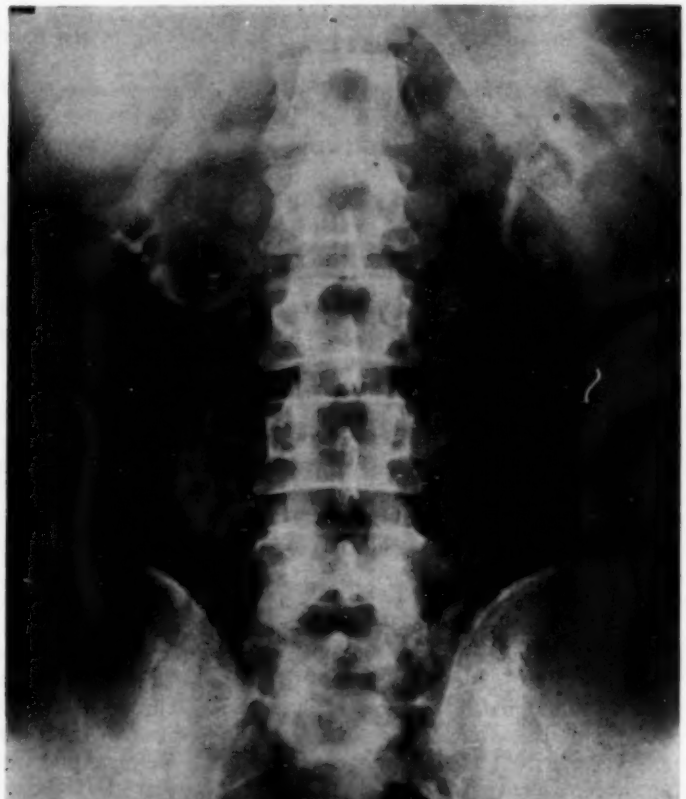

FIG. 1. Intravenous pyelogram showing pressure effects upon the superior pole of the right kidney by a tumor mass.

to 250 mm. systolic and 130 mm. diastolic during the manipulation necessary to removal. With ligation of the pedicle, the blood pressure promptly fell to shock levels. Intravenous plasma and two 50 mg. intravenous injections of ephedrine brought the reading to 100 to 80 mm. Hg systolic and 70 to 50 mm. diastolic within three minutes. Postoperatively, the blood pressure did not fall below 95 mm. Hg systolic and 55 mm. diastolic, and the pulse rate varied between 100 and 125. Convalescence was rapid and uneventful; the patient was out of bed on the second postoperative day and went home on the tenth postoperative day.

Daily blood pressure recordings for some time thereafter and monthly checkup measurements to date (February, 1947) have not been greater than 130 mm. Hg systolic and 70 mm. diastolic. The patient complained, for about two weeks, of coldness and blueness of his hands and feet, but this symptom disappeared after the administration of 0.1 gram of papaverine four times daily for 10 days. The eye grounds returned to a normal appearance, and the phenolsulfonephthalein excretion was 68 per cent in one-half hour and 77 per cent in one hour, with a total two hour excretion of 77 per cent on October 29, 1946. The patient has had no further attacks and his sense of well-being and libido are completely restored.

*Pathology Report.** "The tumor is a globular but somewhat irregular, encapsulated mass, weighing 298 grams. Upon the surface, small, pale brown areas, evidently adrenal cortical tissue, can be identified. Upon section, the tumor tissue appears grayish white in some areas and reddish brown in others. The latter discoloration appears to be due to degeneration and hemorrhage. Two cysts are present; these occupy the central half of the tumor, and they are filled with bloody fluid which coagulates upon standing.

"Microscopic examination of the tumor shows a marked variation in the shape of the cells, some being round and oval while others are polygonal. Some of the cells appear light in color, almost hydropic, while others are small and dark staining. There are no definite anaplastic changes seen. The tissue which was fixed in chrome salts has become brown in color. The pathological diagnosis is benign pheochromocytoma (adrenal)."

The tumor contained eight grams of adrenalin in 200 grams of tumor tissue (equivalent to eight liters of a 1:1000 solution of epinephrine). Ninety-eight grams were fluid with a concentration of 100 mg. to 0.1 per cent. The concentration of adrenalin was equal to 4.0 per cent of tissue by weight.†

Discussion

The patient's reactions to intravenous injections, first of 2 c.c. of a saline solution containing 0.025 mg. of histamine phosphate, then of a solution containing 400 mg. of tetraethylammonium bromide, and finally of 2 c.c. of saline, are compared in figures 2 and 3.

Within one minute after the administration of histamine, the patient developed a typical attack, associated with a rise in blood pressure from 160 mm. Hg systolic and 105 mm. diastolic to 280 mm. systolic and 160 mm. diastolic. The reading returned approximately to normal within five minutes. The pulse rate rose from 94 to 116 and then fell to 96. Although the resting blood pressure was somewhat higher before tetraethylammonium bromide was given, the response was just as pronounced and lasted considerably longer. The reading rose from a basal level of 175 mm. Hg systolic and 105 mm. diastolic to 270 mm. systolic and 160 mm. diastolic in 30 seconds, and the elevation lasted 15 minutes. The pulse rate rose from 75 to 130 and returned to 90. The decrease in the blood pressure when the patient changed from a supine position to standing erect was dramatic, the reading falling from 230 mm. Hg systolic and 125 mm. diastolic to 95 mm. systolic and 80 mm. diastolic. When the 2 c.c. injection of saline was given, no detectable change in the blood pressure or pulse rate occurred.

* Dr. George K. Higgins, Head of Department of Pathology, New York Medical College, New York City.

† Testing performed by Dr. David Lehr, Head of Department of Pharmacology, New York Medical College, New York City.

On October 15, 1946, approximately two months postoperatively, the above tests were repeated and the patient evinced no reaction whatsoever to the injection of histamine, tetraethylammonium bromide, or saline (figure 4).

It is reasonable to assume that the preoperative hypertension found in this patient resulted from the oversecretion of epinephrine, and that the paroxysmal attacks were due to the sudden release of large amounts of epinephrine into the blood stream. Heavy exertion, positional changes, and manipulation of the tumor all resulted in sudden hypertension of high degree, undoubtedly due to release of epinephrine simply by mechanical pressure on the tumor. Preoperatively, the only times when normal blood pressure readings were obtained were

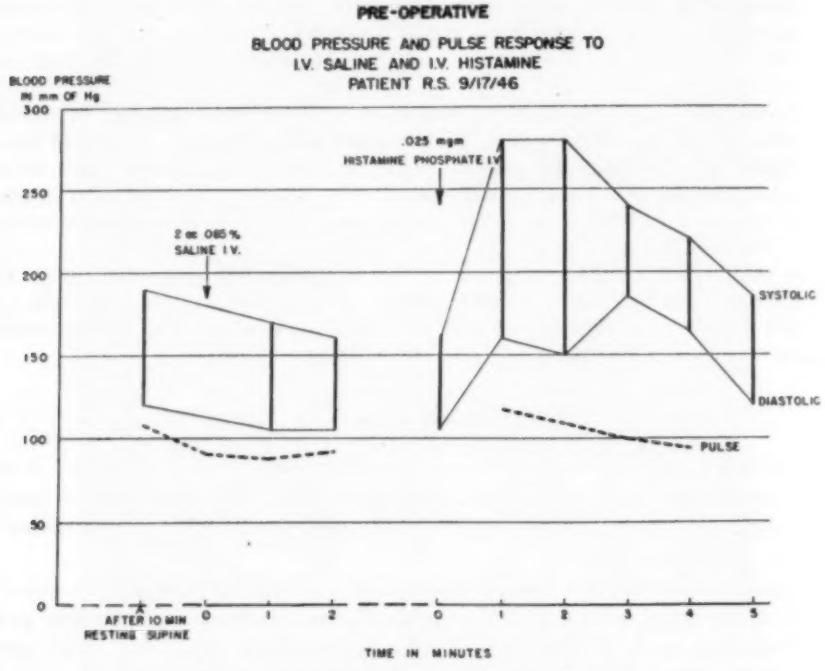

FIG. 2. Graph showing blood pressure and pulse response to the intravenous injection of 0.025 mg. of histamine diphosphate and to the intravenous injection of 2 c.c. of saline.

when the patient had been lying quietly on his back for an hour or more. The effect of massage or pressure in precipitating typical attacks has been emphasized.[1, 3, 5] It is also noteworthy that high concentrations of a pressor-like substance have been found in the blood of patients during seizures.[6]

The release of epinephrine from a pheochromocytoma may be brought about by the dilating action of histamine on the arterioles and capillaries of the tumor. This increases the blood flow through the tumor with resultant outpouring of epinephrine. That histamine may have a direct action on the tumor cells, as it does on the chief cells of the stomach, cannot be affirmed or denied.

Acheson and Moe [7] have demonstrated that tetraethylammonium bromide will block transmission of nerve impulses through the autonomic ganglia. In man, the effects on the cardiovascular system after the administration of 0.2 to 0.5 gm.

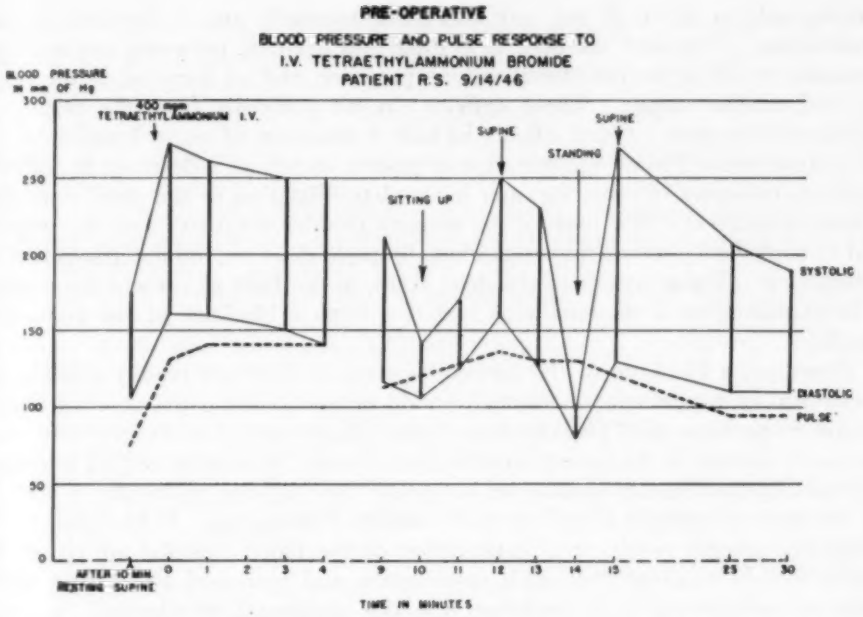

FIG. 3. Graph showing blood pressure and pulse response to the intravenous injection of 400 mg. of tetraethylammonium bromide and to the injection of 2 c.c. of saline. Changes in blood pressure and pulse rate resulting from shifting from a sitting, standing, and supine position are indicated.

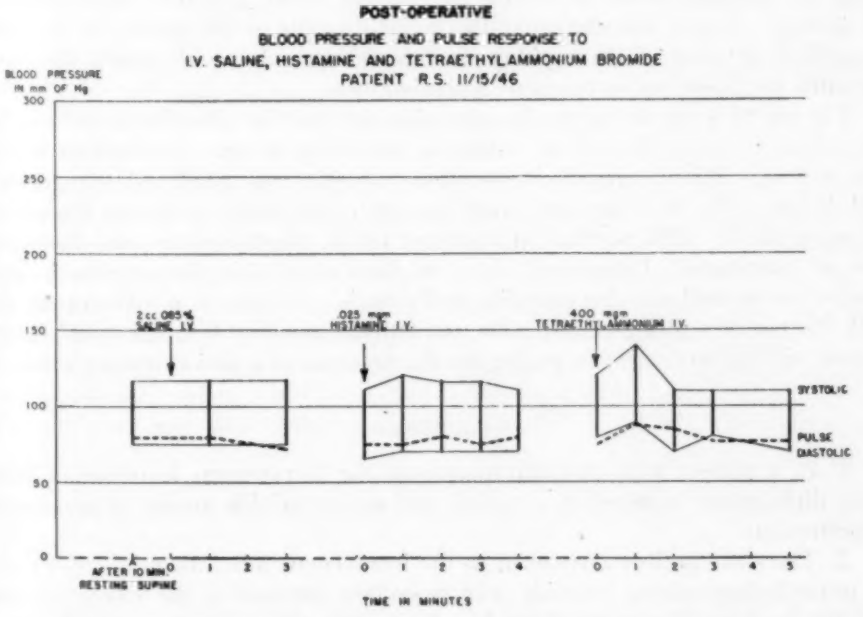

FIG. 4. Graph showing the postoperative absence of response to the intravenous injection of histamine, tetraethylammonium, or saline.

intravenously or up to 20 mg. per kilo intramuscularly are an increase in skin temperature, a transient fall both in systolic and diastolic pressure, postural hypotension, a fall in the peripheral venous pressure, and an increase in the heart rate and cardiac output. These (effects) result primarily from the release of vasoconstrictor tone. Other effects include a cessation of normal peristalsis in the gastrointestinal tract, a diminution in gastric secretion, a decrease in salivary secretion, cessation of sweating, and incomplete dilatation of the pupil with loss of accommodation. The tone of the urinary bladder decreases and the urge to void is abolished. Tetraethylammonium bromide does not inhibit the action of epinephrine. These actions of the drug seem, in the light of present knowledge, to be explained most reasonably as resulting from a blockade of the autonomic ganglia.

However, a blockade of the autonomic ganglia does not readily explain the mechanism of tetraethylammonium bromide in precipitating paroxysmal hypertension in patients with pheochromocytoma. If an excess of epinephrine were constantly present in the patient's circulation, it could be postulated that inhibition by tetraethylammonium bromide of depressor mechanisms under the control of the sympathetic ganglia would result in sudden hyperpiesia. If blockade of the autonomic ganglia results in a denervation of the blood vascular supply of the tumor, loss of vascular tone with vasodilation and increased blood flow might cause an outpouring of epinephrine into the peripheral circulation. A direct vasodilating effect on the arterioles of the tumor would have a similar result. Lyons [8] suggests that the maintenance of renal blood flow in the face of precipitous falls in blood pressure produced by tetraethylammonium bromide can best be explained on the basis of moderate dilatation of the renal arterioles, brought about by blockade of the autonomic ganglia—in effect, a partial denervation of the kidney. Direct stimulation of the secretory cells of the tumor by the drug is unlikely in view of the rapidity (within 30 seconds) with which the blood pressure rises after its intravenous administration.

The use of tetraethylammonium bromide as a test for pheochromocytoma has one advantage over the use of histamine, according to our observations in this one patient. When tetraethylammonium bromide was employed, dangerously high levels of the blood pressure could be controlled simply by having the patient sit up or stand. This resulted in a prompt fall in blood pressure and disappearance of symptoms. Lyons and his co-workers noted this phenomenon in their studies on normal and hypertensive individuals. Hence, it would appear that with the use of a tilting bed or table, tetraethylammonium bromide could be employed with perfect safety in testing for the presence of a pheochromocytoma.

Conclusions

1. In a patient with pheochromocytoma the intravenous injection of histamine diphosphate resulted in a typical and uncontrollable attack of paroxysmal hypertension.

2. The same patient responded to the intravenous administration of 400 mg. of tetraethylammonium bromide with a sudden increase in the blood pressure, but the level and duration of the blood pressure rise could be controlled by a change in the patient's posture.

3. The use of tetraethylammonium bromide, therefore, appears to be a safe test for the presence of a pheochromocytoma.

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SICKLE CELL DISEASE: REPORT OF A CASE WITH CEREBRAL MANIFESTATIONS IN THE ABSENCE OF ANEMIA *

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Sickle cell disease was originally described by Herrick [1] in 1910, as anemia with sickle-shaped erythrocytes. During a crisis of sickling these characteristic cells become wedged in capillaries, often producing thrombosis. In the past 20 years increasing attention has centered about the histopathology of sickle cell disease, particularly with reference to the vascular thromboses so frequently noted. This vascular occlusive phenomenon results in a protean symptomatology dependent upon the vessels occluded. Although the cerebral manifestations of the disease were undoubtedly previously noted, the first report was that of Sydenstricker, Mulherin, and Houseal [2] in 1923. This was followed by isolated case reports.[3–22] In 1940 Hughes, Diggs, and Gillespie [23] reviewed the literature on the cerebral manifestations of sickle cell disease and added six cases of their own. Since 1940 additional case reports [24–28] have increased the total reported cases to forty.

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In 1940 Bauer [29] stated that, "The disease known as sickle cell anemia might better be named sickle cell disease, because anemia, though the best known and most frequent sign of this disease, is not the essential and not the most dangerous one." Thus, he suggested that the phenomenon of vascular occlusion could occur independently of anemia as a result of the sickling tendency alone. This concept was further amplified by Bauer and Fisher [30] in 1943.

The case to be presented is of interest because, in a review of the literature of the cerebral manifestations of sickle cell disease, no case has been reported without anemia in which the clinical and pathological manifestations were predominantly cerebral.

Case Report

A 20 year old colored male was admitted to the United States Naval Hospital, Newport, Rhode Island, on August 20, 1944, complaining of dizziness and pain in the right arm. He was drowsy and his response to questioning was abnormally slow. The temperature was 100° F., pulse 100, and respirations 28. Past and family histories were negative. Physical and neurological examinations showed only fever, slowness of cerebration, and drowsiness.

Because of the impaired sensorium a spinal puncture was done. The spinal fluid was slightly, but homogeneously blood-tinged, and under a pressure of 120 mm. of water. There was no growth on culture. Spinal fluid chemistries were as follows: sugar, 75 mg. per cent; total protein 88.8 mg. per cent.

For the next three days his only symptom was mild generalized headache. The temperature ranged from 97° F., to 100.8° F. Blood studies were as follows: Hemoglobin, 15 grams (Sahli); erythrocytes 4.95 million; leukocytes 13,800 with 70 per cent polymorphonuclear neutrophiles, and the remainder of the differential formula, normal. The serological test for syphilis was negative. Tests for sickling were not done.

On the fourth hospital day he had a generalized convulsion. The temperature rose rapidly to 108° F., rectally, and the pulse to 220. During the next eight days his condition remained static. He was in deep coma. The temperature varied from 101° F., to 105° F.; pulse from 110 to 180, and respirations from 35 to 80 per minute. Repeated neurological examinations are summarized in the following findings. Cranial nerves: The fundi revealed no abnormality of either discs or vessels. The pupils were equal in diameter and reacted sluggishly to light. There was a spontaneous nystagmus, horizontal in type. The remainder of the cranial nerves showed no abnormality. Motor system: Sporadic clonic convulsive movements of the right side of the body were noted. The left arm remained in a state of tonic extension. Intermittent fibrillations were noted in the muscles of the right thigh. Deep tendon reflexes were hyperactive on the left side and normal on the right. All superficial reflexes were absent. There was no response to plantar stimulation. Sensory system: None of the modalities of sensation could be tested.

Treatment consisted of oxygen therapy, sedation with the anticonvulsants, and general supportive measures. Ice caps, alcohol sponges, and ice water enemata were employed to combat hyperthermia. In spite of these measures he suddenly died on the thirteenth day following admission.

An autopsy was performed immediately after death. The body was that of a tall, thin, colored male, 20 years of age. Examination of the skin disclosed no abnormalities. No hemorrhages were noted. A summary of the gross pathologic findings follows: There were 1000 c.c. of cloudy fluid in the left pleural cavity. A small, recent hemorrhagic infarct was seen at the base of the left lung. The spleen weighed 110 grams and presented a friable cut surface. The liver weighed 1850 grams and showed a smooth, reddish-brown, lobulated cut surface. The remainder of the abdominal and thoracic viscera were grossly normal.

Microscopic studies of the liver, spleen, heart, lung, and kidneys, showed the vessels packed with sickled erythrocytes, estimated to be almost 90 per cent of the total number present. Occasional normoblasts were observed.

The epicardium was smooth. The cardiac fibers were fragmented in many places, and throughout the myocardium there were found many areas of focal degeneration.

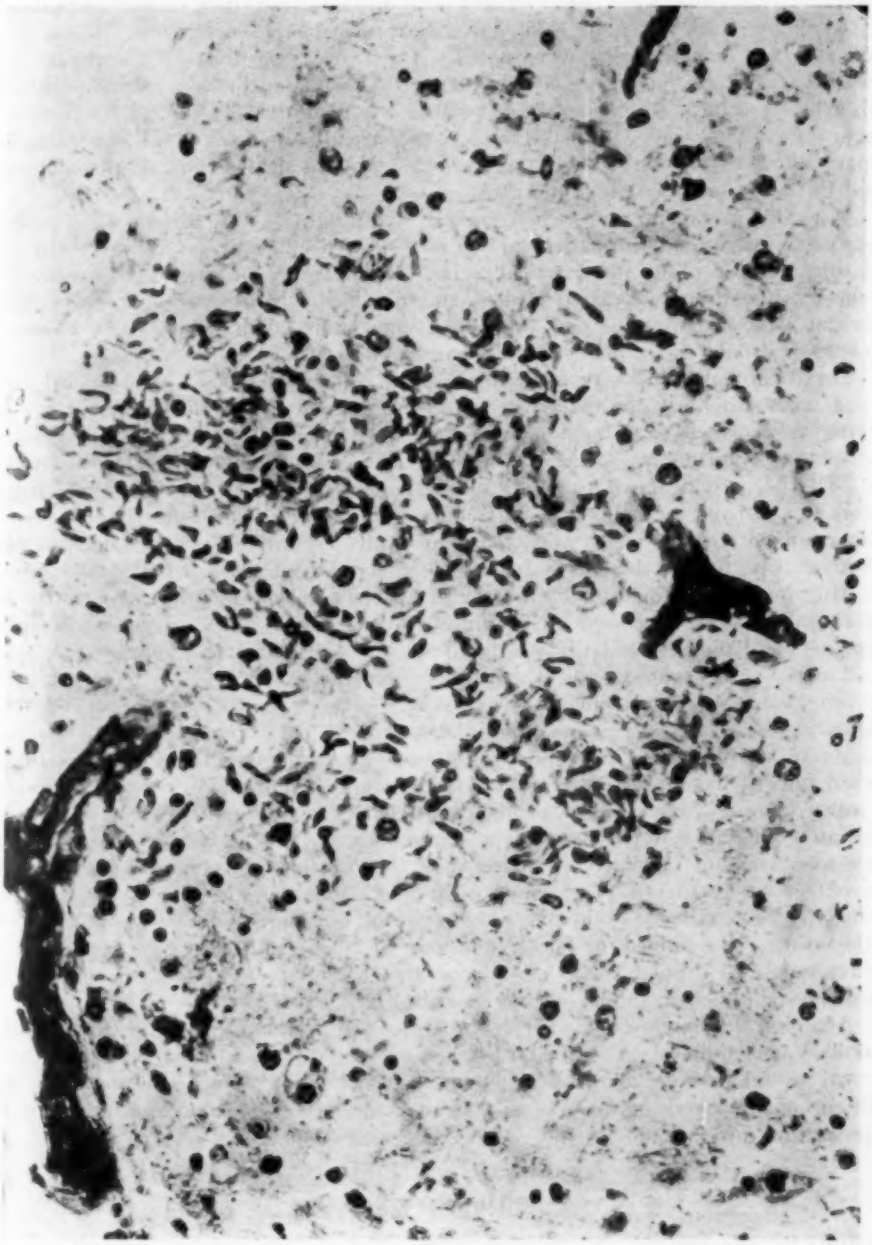

FIG. 1. Photomicrograph showing closely packed sickled erythrocytes in an area of hemorrhage.

In these areas the muscle fibers had disappeared, leaving only the sarcolemma and occasional pyknotic nuclei. There was much interstitial edema. Within the kidneys numerous punctate hemorrhages were found. In the liver the architecture was preserved. There was slight cloudy swelling of the cord cells. The hepatic and Küpffer cells showed mild pigmentary changes. No abnormalities of the splenic capsule or trabeculae were seen. There was diffuse congestion of the sinusoids in the red pulp. This was most pronounced near the splenic corpuscles. A few scattered areas of hematopoiesis were noted. There was questionable endothelial proliferation within the splenic vessels. The pleural surface of the left lung was covered with a heavy deposit of leukocytes and fibrin. A histologically typical fresh hemorrhagic infarct was seen within the lung tissue beneath this area. Although the pulmonary arteries, veins, and capillaries were packed with sickled cells, no thrombi were noted in the vessels examined microscopically.

When the calvarium was opened, no bony abnormalities were observed. The dura was intact. Examination of the brain in situ showed extreme congestion, tortuosity, and dilatation of all of the cortical veins, which were cord-like and tense. The cerebral convolutions appeared swollen and flattened. Numerous scattered subpial, petechial hemorrhages were seen over the frontal and occipital lobes. An excess of cerebrospinal fluid was present in the subarachnoid space.

Serial coronal sections through the brain revealed numerous wedge-shaped areas of yellowish softening surrounded by confluent groups of petechial hemorrhages involving the cortical gray matter and the adjacent white matter in both cerebral hemispheres (figure 1). These hemorrhagic areas varied in diameter from 1 to 3.5 cm. The deep cortical white matter of the cerebrum, as well as the basal ganglia, midbrain, pons, and cerebellum, revealed only scattered petechial hemorrhages. A few fresh confluent hemorrhages were found in both cerebral peduncles. The medulla and a small portion of the cervical spinal cord showed no gross pathologic change.

Microscopic examination of the sections of the cerebral cortex showed an organizing thrombotic process distinctly limited to the vessels in the subarachnoid space, pia mater, and the vessels lying within the cortical gray matter. Innumerable veins of all sizes were occluded. These thrombi were distinctly ante mortem. Many of the veins were surrounded by broad cuffs of confluent hemorrhage. Some of these hemorrhagic areas appeared recent; others showed partial resolution. The endothelium of the cortical veins had proliferated, appeared loosened, and was turned inward toward the lumen of the vessel to become incorporated within the thrombus in many places. Much edema of the vessel walls was present and there was an associated infiltration of polymorphonuclear leukocytes, lymphocytes, and macrophages. Numerous areas of partially organized subarachnoid hemorrhage were seen. There was extensive destruction of ganglion cells throughout the cortex. Glynn stains for bacteria were negative. Following the suggestion of Wade and Stevenson,[26] sections of the cortex were stained for fat. Numerous fat laden gitter cells were found, but no intravascular fat droplets were seen. Sections taken at other sites throughout the brain showed a picture similar to that described above.

Anatomical Diagnosis: Sickle cell disease; congestion, spleen; evidence extramedullary hematopoiesis; endothelial hyperplasia, cortical vessels, marked; thrombosis, cortical veins; perivascular and confluent interstitial hemorrhages, cortex, marked; with encephalomalacia, secondary, mild; pulmonary infarct, recent, hemorrhagic; focal degeneration, myocardium; hemorrhages, petechial, kidney.

Discussion

Initially the patient presented a vague clinical syndrome composed only of mental retardation, drowsiness and slight fever. The physical examination was

FIG. 2. Segment of cerebral cortex showing confluent petechial hemorrhage.

negative. The spinal fluid contained fresh blood. The clinical syndrome was that of an atypical spontaneous subarachnoid hemorrhage. On the third hospital day signs of cerebral cortical irritation appeared in the form of generalized convulsions. This was rapidly succeeded by clinical signs of diencephalic damage.

At this point it was evident that the syndrome resulted from diffuse involvement of the central nervous system. There then developed an acute diffuse hemorrhagic encephalitis, the etiology of which remained obscure. Diagnosis was not established until autopsy, when the sickled intravascular erythrocytes, and the associated vascular and thrombotic lesions were demonstrated.

The entire pathologic process in this case was vascular in nature. At no time was there laboratory or clinical evidence of anemia or of a hemolytic crisis. The major lesions were limited to the cortical veins which were filled with laminated, recent thrombi composed of sickled red cells. The pathologic process which resulted from this occlusion was that of an intense passive congestion of the cortical veins and capillaries with subsequent rupture or erythrocytic diapedesis which produced diffuse, confluent destructive cortical hemorrhages (figure 2). These hemorrhages had been present for a length of time sufficient for mild early reactive gliosis to occur. No arterial occlusions were observed.

This intense passive congestion produced a stagnant anoxia which further relaxed the vessel walls. This process in turn resulted in increasing hyperemia and vascular permeability, thus augmenting the bleeding caused by the venous thrombotic lesions. The evident venous origin of the cerebral lesions would tend to discredit the theory that the cortical hemorrhages seen in the cerebral manifestations of sickle cell disease result from fat emboli.[26]

This case demonstrates the value of the routine examination of the blood (and bloody spinal fluid, if present), for sickling in any patient presenting obscure neurologic signs which might be explained by diffuse, or focal venous thromboses. It is important to consider the diagnosis of sickle cell disease in any obscure neurologic lesion in the negro.

Anemia is not necessarily a part of the picture of sickle cell disease, and this case demonstrates that it is not necessarily a part of sickle cell disease in which the symptomatology is predominantly cerebral. A blood dyscrasia might have been suspected if anemia had been present.

Summary

A case of sickle cell disease without anemia is presented in which the signs and symptoms were solely referable to the central nervous system. The value of routine sickling tests on all patients presenting evidence of subarachnoid bleeding or neurologic symptoms which might be explained on the basis of a diffuse vascular thrombotic process has been emphasized.

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SICKLE CELL ANEMIA WITH STRIKING ELECTROCARDIOGRAPHIC ABNORMALITIES AND OTHER UNUSUAL FEATURES, WITH AUTOPSY *

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THIS case of sickle cell anemia with autopsy is considered worthy of reporting because of the following unusual features: (1) the symptomatology simulating coronary occlusion, with gross electrocardiographic evidence compatible with this condition, in the absence of any histopathologic evidence of myocardial damage other than simple cardiac hypertrophy and dilatation with moderate interstitial edema; (2) the marked sickling of erythrocytes even in the usual blood smear; (3) the coexistence of duodenal ulcer which evoked abdominal pain simulating that often seen in hemolytic crises of sickle cell anemia; (4) the extraordinarily small size of the spleen (5 grams).

CASE REPORT

History. A 22 year old negro was admitted August 13, 1946 to a Naval Hospital 11 hours after the onset of a severe substernal chest pain. Eight days prior to the onset of the chest pain, the patient developed cramp-like intermittent lower abdominal pain, anorexia, vomiting, fever, and chilly sensations associated with yellow sclerae and dark urine. On the morning of admission while at work he was suddenly seized by severe substernal pain. The pain did not radiate or subside and, at the time of admission to the hospital from a Naval dispensary, was more severe than at its onset. Physical examination soon after the onset of the pain disclosed an acutely ill patient with deeply jaundiced sclerae, a heart enlarged to the left and right and a basal systolic murmur loudest in the pulmonic area and along the left border of the sternum. The blood pressure was 174 mm. Hg systolic and 114 mm. diastolic in the right arm and 180 mm. systolic, 120 mm. diastolic in the left arm. At this time a chest film showed the heart enlarged in all diameters, predominantly the left ventricle, with increased hilar markings in the right upper lobe. Examination of the blood showed a marked anemia and sickling. The temperature was 98.4°, pulse 88 and the respirations 24. The impression was sickle cell anemia with hemolytic crisis, and accordingly the patient was transferred to the hospital.

The family history revealed no evidence of sickle cell anemia in other members of his family. Blood studies at this hospital on an older brother failed to reveal even a sickle cell trait.

The past history revealed that the patient was hospitalized as a child because of

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The opinions herein stated are those of the authors and not necessarily those of the Medical Department of the U. S. Navy.

jaundice of unknown cause. Subsequently he had attacks of abdominal cramps but never severe enough to prompt medical attention.

After the patient entered the Navy in 1942 he was hospitalized because of jaundice, joint pains, and abdominal cramps. He was found to have sickle cell anemia. He was transfused several times and was subsequently discharged from the Naval service. In 1944 and 1945 the patient had two episodes of similar symptomatology for which hospitalization was required.

Physical Examination. On admission, examination revealed a well developed, emaciated young negro with a tower-shaped skull, deeply icteric sclerae and pale mucosae, appearing acutely ill, lying flat in bed. At this time, the blood pressure was 144 mm. systolic and 80 mm. diastolic, the temperature was 100.4°, the pulse 78 per minute and respirations 18 per minute. A grade IV (I–VI) basal systolic murmur was heard, at the greatest intensity in the pulmonic area. The radial and brachial arteries were readily palpable and extremely firm. There was tenderness in the midepigastrium with moderate generalized splinting of the abdomen. Several pretibial oval shaped scars were present over the lower extremities.

Laboratory Findings. Routine stained blood smears showed up to 20 per cent sickled cells, whereas 100 per cent sickled cells were observed in repeated wet preparations after 24 hours. A blood count showed 2.5 million red blood cells, with 7.2 grams of hemoglobin, and a white blood cell count 15,100 with an essentially normal differential count. The red blood cell fragility test showed beginning hemolysis at 0.40 per cent sodium chloride which was incomplete even in distilled water (control hemolysis began at 0.44 per cent and was complete at 0.28 per cent). A van den Bergh test was indirect and a serum bilirubin was 15 mg. per cent. Urine urobilinogen was positive up to 1–100 dilution. Urinalysis showed a specific gravity of 1.013, 50 mg. per cent albumin, 3 to 5 white blood cells and 8 to 12 red blood cells per high power field. The Kahn test was negative for syphilis. Erythrocyte sedimentation rate (Cutler) on August 13, 1946 was 9 mm. per hour.

An electrocardiogram on admission (figure 1) showed a rate of 80 with regular sinus rhythm, PR interval of 0.13, left axis deviation, with T_1 low, M-shaped and flattened, T_2 isoelectric, T_3 inverted and T_4 upright. It was interpreted as evidence of possible myocardial damage.

Teleroentgenogram showed a heart grossly enlarged in all diameters, especially in the region of the left ventricle.

Clinical Course. The substernal pain was only partially relieved by morphine. After the patient was kept in an oxygen tent for four days, he was free of chest pain but complained of pain in the midepigastrium, especially at night, as well as pain in his knees and elbows. The epigastric pain was relieved by sodium bicarbonate and by milk. He stated that he was accustomed to taking these in large quantities for the past several months. The patient was placed on a modified Sippy regime with some benefit, although it was undecided as to whether the abdominal pain was a result of the hemolytic crisis and favorably influenced by alkaline therapy, or due to a peptic ulcer. Fluoroscopy showed no abnormalities other than a heart enlarged in all diameters. After the crisis had subsided a transfusion was given with no apparent signs of reaction or definite benefit. Gastrointestinal studies were ordered but before the patient could recover sufficiently to warrant radiographic examination he had another severe crisis on the forty-first hospital day. He complained of severe substernal, epigastric, lumbo-sacral, knee and lower leg pain. The heart was extremely overactive with a bounding pulse and heaving precordium. The pulmonic murmur was increased to Grade V and there was a systolic thrill in the pulmonic area. The patient was given morphine therapy in ¼ gr. doses every two to four hours, with only partial control of pain. He was again placed in an oxygen tent. A second electrocardiogram on August 15, 1946 (see figure 1), showed some progression of the

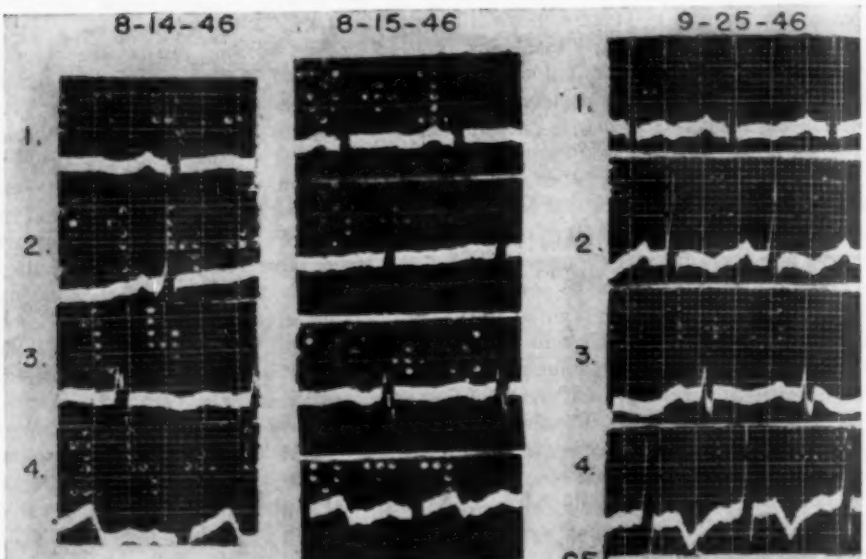

FIG. 1. Successive electrocardiographic tracings.

changes noted in the initial tracing of August 14, 1946. The T-waves in Lead I were further depressed, T_2 isoelectric, T_3 inverted and T_4 showed terminal inversion with decreased amplitude. Chest leads showed T-waves inverted in CF 5 and 6. The electrocardiogram on September 25, 1946 (figure 1), the day following the onset of the second crisis, showed further gross changes: T-waves in Lead I were diphasic, T_2, T_3 and T_4 were inverted, and the chest leads showed inversion of T-waves in CF 4, 5, and 6. The tracing of October 1, 1946 (figure 1), six days following the onset of the second crisis and three days after he had improved, showed T-waves in Lead I again upright but of low amplitude, with T_2 and T_3 inverted and T_4 again upright.

The erythrocyte sedimentation rate (Cutler) on September 6, 1946 was 12 mm. per hour. On September 25, 1946 it was 27 mm. per hour and 4 mm. in 5 minutes. The temperature fluctuated irregularly from 98° F. to 101° F. for the first two weeks and then ranged from 97.5° F. to 100.5° F. for the next four days during the second crisis. It then gradually dropped to normal. On October 8, the patient entered his third severe crisis and his temperature rose and remained at 102° F. for 24 hours and then rose to 103° F. on the day of his death, October 10, the fifty-eighth hospital day. The pulse previously had averaged 85 per minute, rising to 100 during the two previous crises. It ranged from 110 to 120 per minute during the last 24 hours. The respirations which had averaged 20 to 25 per minute rose to 30 to 45 per minute during the last day. These observations plus the findings of moist râles throughout the chest indicated a terminal pneumonia rather than congestive failure, as the contributory cause of death.

Autopsy examination revealed the following pertinent findings:

The heart weighed 455 grams and showed right and left ventricular enlargement. There was moderate dilatation of both auricles. Eighteen representative sections were examined microscopically. These included ten from the area of questionable pathology as indicated by the electrocardiograms. All sections revealed moderate hypertrophy of some muscle fibers. Three quite small areas of fibrosis were noted. There was moderate interstitial edema. Occasional clumps of about five Anitschkow cells were observed. These were in the interstitial tissue about the vessels and capillaries. There was no evidence of thrombosis, endarteritis, polymorphonuclear or fatty infiltration or degeneration.

The lungs, grossly and microscopically, revealed the findings typically associated with bronchopneumonia.

The spleen weighed five grams. It measured 6 by 1.5 by 0.3 cm. It was light green and quite firm. Microscopic examination revealed complete replacement of the normal parenchyma by irregular masses of hyalinized fibrous tissue and thick walled fibrotic blood vessels. The fibrous tissue and vessel walls were infiltrated with amorphous material which contained calcium and iron. In the vessels this material was located particularly in the internal elastic membrane. The arteries and arterioles were distorted by these hemosiderotic masses. No hemopoiesis was observed.

The abdominal lymph nodes showed marked hypertrophy grossly. Microscopically hyperplasia of the reticulo-histiocytic elements was noted.

The bone marrow of the skull, sternum, ribs, vertebrae, femur and tibia was markedly hyperplastic. The hyperplasia had caused marked thinning of the inner and outer tables of the skull. The marrow of about one-half of the ribs was hyperplastic while the marrow of the others showed extensive fatty infiltration. One area of the cortex of the anterior surface of the upper third of the right tibia was thinned to 0.1 cm. In the center of the thinned area there was a thrombosed penetrating vessel. Surrounding the vessel and extending over a radius of 3 cm. was a collection of dark brown semi-fluid material. This was located between the cortex

and periosteum. Microscopic examination proved it to be essentially normal bone marrow.

The liver weighed 2270 grams. It was moderately congested. The Küpffer cells contained large amounts of iron pigment. The architecture was well preserved.

The kidneys showed multiple old and recent infarcts. Microscopic examination revealed moderate congestion of the parenchyma and extensive iron deposition in the convoluted tubules.

The duodenum revealed a 1.0 cm. in diameter active ulcer.

The blood in all the organs showed marked sickling and many nucleated red blood cells.

Discussion

In contrast to the gross electrocardiographic abnormalities in our case, an analytical study of electrocardiograms of 25 patients with sickle cell anemia by Winsor and Burch [1] revealed no inversion of the T-waves in Lead I (average amplitude 1.7 mm.) or Lead II (average amplitude 4 mm.), and upright T_3 waves in 70 per cent of the cases, with no sharp inversion in any case. In the chest leads the average amplitude of the T-waves in Leads CF-1, CF-2, and CF-3 was − 3.4, − 3.6 and 1.5 mm. respectively. In Leads CF-4, CF-5 and IVF the T-waves were inverted or diphasic in 40 per cent of the subjects. In Case 16 of their series, one of four followed by serial electrocardiograph for three to four years, there were progressive abnormal changes but the other three were normal. In Case 16 the T-waves in Lead IV were normal and upright on August 14, 1939 and November 12, 1941 but deeply inverted on December 3, 1941 and May 3, 1943. They do not state whether the patient had a crisis during his electrocardiographic changes or whether reversion toward normal occurred. Twenty per cent of 25 cases showed significant electrocardiographic changes when single tracings were studied in the usual manner; 4 per cent showed a low T_1.

Klinefelter [2] found no frank electrocardiographic evidence of myocardial damage, on the other hand, in his 12 patients with sickle cell anemia.

Zimmerman and Barnett [3] have reported a case of sickle cell anemia simulating coronary occlusion. This case was that of a 30 year old negro male with proved sickle cell anemia and a coronary-like syndrome. Severe substernal pain radiating to both arms was accompanied by profuse perspiration, nausea and vomiting. The admission electrocardiogram revealed an inverted T-wave in Lead IVF and broad and low T-waves in Leads I and II without any significant ST segment deviation. In a second tracing taken three days after admission the T-waves in IVF were M-shaped and the T-waves in Lead II diphasic. The third electrocardiogram taken 16 days after admission and shortly before discharge, showed an upright T_4 with an increase in amplitude of the upright T-wave in Leads I and II. The electrocardiographic changes in the case we are reporting were more gross than those of the above case, especially in the tracing of September 25, 1946 (figure 1) which was taken one day after the onset of the second severe crisis. However, in our case, as was noted in their tracings, the pattern reverted toward normal much sooner than one would expect in the case of an infarction. The tracing of October 1, 1946 which is reverting to normal was taken six days following the previous tracing of September 25, 1946 and only three days after the remission from the second crisis.

In the aforementioned study of 25 patients with sickle cell anemia, nine were autopsied, three dying in congestive heart failure. All nine cases showed, in ad-

dition to variable degrees of cardiac hypertrophy and dilatation, one or more of the following pathological changes: interstitial edema, myocardial degeneration, vacuolated sarcoplasm, Zenker's degeneration, polymorphonuclear interstitial infiltration, and in one instance, obliterative endarteritis of the coronary and pericardial vessels. The heart weights ranged from 225 to 440 grams.

Winsor and Burch [1] state further that while cardiac hypertrophy and dilatation, often associated with fatty degeneration, is common in a variety of severe anemias, there are certain changes in sickle cell anemia which are not due to anemia. They state that changes in the heart may be manifestations of arteritis and endarteritis with thrombosis.

These pathologic cardiac findings were in contrast to those in our case which merely showed simple hypertrophy, slight dilatation, and moderate interstitial edema, despite careful search for other changes, including 10 sections through the left ventricular wall at the site in which myocardial damage was anticipated from the electrocardiographic changes. The three small areas of fibrosis might be expected with the degree of hypertrophy noted. No significant interpretation can be attached to the Anitschkow cells, but it is believed that they bear no relation to the sickle cell anemia.

Wintrobe,[4] referring to the studies of Carter and Traut,[5] and Ellis and Faulkner,[6] has summarized the commonest electrocardiographic changes, often reversible, occurring in severe anemia of any type as depression of R-T (S-T) junction with a U-shaped deformity of the S-T segment and flat or inverted T-waves, but without corresponding changes in QRS complex. He states that these electrocardiographic changes have been similar to those in sickle cell anemia. He stresses the fact that the heart in sickle cell anemia, which is enlarged in at least 76 per cent of the cases, represents the extreme form of the "heart in anemia," whatever the mechanism may be. He refers to various possible etiologic factors such as increased work load, chronic myocardial anoxia, the circulatory stasis in the internal organs presumably due to sickling, the characteristic extreme tortuosity of the blood vessels, disseminated occlusions of small pulmonary arteries leading to cor pulmonale, etc. At any rate, with respect to the heart in anemia in general, he is of the opinion that anemia of short duration results in cardiac dilatation that can be completely overcome by relief of the anemia (cf. similar reversibility of electrocardiographic changes), whereas in cases of long duration hypertrophy takes place.

In view of the above consideration, it seems reasonable to conclude that in our patient, whose anemia remained relatively stable at 6 to 7 grams of hemoglobin, the augumented electrocardiographic abnormalities during crisis were due, in large measure at least, to the relatively increased myocardial anoxia imposed by the greater work demands on the heart incident to the fever, pain, etc. which occurred with each crisis. This case was considered no exception to the general observation [4] that sickle cell anemia patients are not improved by blood transfusion. Furthermore, the cardiac pathology of simple hypertrophy, etc. in this case was little more than that commonly seen in other severe anemias.[5, 6]

The lack of more cardiac pathologic changes in our case was all the more surprising in view of the marked sickling, up to 20 per cent on the stained smear, an observation which is uncommon,[7] occurring only in very severe cases.

Various causative factors in the abdominal crisis of this disease have been suggested, such as gall stones,[8, 9] arterial thrombosis of the liver,[10] the commonly

observed hypochlorhydria,[11, 12] splenic infarcts,[12] and root pains on the basis of marked changes in the vertebrae.[13] In our patient undoubtedly some of his pain was caused by his duodenal ulcer, which was not strongly suspected. We have been unable to find any reported case in which a peptic ulcer coexisted with sickle cell anemia, which leads us to assume that no causal relation exists. However, the infarctions frequently observed in other organs in this disease might offer a theoretical reason for this patient's ulcer, although thrombotic occlusion of this deep chronic ulcer was not demonstrable. The alkaline therapy given to him ameliorated his epigastric pain to the extent that he continually asked for sodium bicarbonate and milk; his lower abdominal pain and flank pain, however, were not relieved. It is of interest here that Levy and Schnabel [14] reported immediate cessation of all abdominal pain in a patient with sickle cell anemia on two occasions following administration of sodium bicarbonate, potassium citrate and potassium sulfocyanate, but no change in the sickle cell count was observed at these times.

The smallest spleen in sickle cell anemia has been reported as weighing 2.4 gm. To our knowledge, the spleen in our case which weighed 5 grams, is the second smallest to be reported. The specific pathological changes observed in larger spleens by Rich [16] and Diggs [17] were not found in our case, presumably because of the extensive fibrosis.

Summary

An unusual case of severe sickle cell anemia is presented. The gross electrocardiographic changes, even though quickly but partially reversible after the hemolytic crises, led us to expect rather marked myocardial damage, but an autopsy revealed only the simple hypertrophy and moderate interstitial edema often seen in a variety of severe anemias.

A coexisting duodenal ulcer was a confusing element in the clinical picture.

The weight of the spleen in this case was 5 grams, the second smallest reported in the literature.

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HYPERTHYROIDISM OCCURRING AT AN EARLY AGE IN DISSIMILAR TWINS *

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HYPERTHYROIDISM is a disease which may occur during childhood and adolescence. Pemberton and Black [1] have reported 189 children of 14 years and under who were observed at the Mayo Clinic while suffering from this disease. Over 80 per cent of their patients were between the ages of 10 and 14 years, and they found the disease to be rare before the age of nine years. A perusal of the literature reveals a sufficient number of articles on the subject to justify a brief discussion of the salient points of the disease in childhood and adolescence before presentation of the two cases which instigated this report. The statements made refer to patients 14 years of age and under.

In all series female patients predominate, the sex ratios in three comparable series [1, 2, 3] averaging 5.7 to 1. Some authors [4] believe that a family history of thyroid disease is unusually frequent in patients in this age group.

With few exceptions the symptomatology parallels closely that of the adult disease.[5] An abrupt onset is frequent, and emotional instability may be a most troublesome accompaniment.[8] This was strikingly evidenced in one of the cases here reported. Several authors have been impressed with the frequency of exophthalmos. Helmholtz [5] found this condition present in 83 per cent of his cases; Greene and Mora [10] in 81 per cent of their cases. Crile and Crile [9] concluded that exophthalmos was more frequent and more severe in children and that failure to recede postoperatively was not uncommon.

For many years it has been realized that a normally functioning thyroid gland is essential for normal growth, and hyperthyroidism occurring before the attainment of growth maturation is frequently associated with an increased rate of growth.[3, 6, 7] Striking precocious skeletal development at the expense of soft tissue development may occur,[6] and Hertz [7] has observed a case showing such a striking degree of growth as to be termed "thyrotoxic gigantism." Hertz et al.[7]

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have studied the problem of hyperthyroidism and growth and conclude that the excess of hormone apparently does not produce early or late epiphyseal closure, so that the acceleration occurs only during the normal growth span.

Burke [10] has reported a hyperthyroid child who after four and one-half months of thiouracil therapy was showing a satisfactory response. Prior to the introduction of this drug, and there is as yet no other report available on its use in patients of this age, subtotal thyroidectomy following careful preoperative preparation with iodine was the procedure advised in a vast majority of the cases. The possibility of permanent personality changes due to the associated emotional instability, the frequency of abnormal growth rates, and the natural lack of coöperation on the part of the patient usually preclude long term medical therapy. Severe operative and postoperative reactions are frequent, and the necessity of multiple stage operations is increased. Some authors [1, 12, 13] have stressed the frequency of postoperative hypothyroidism, but in many cases continued observation has shown this to be a transient phenomenon. Others stress the frequency of recurrence or persistence of the disease,[11] and these appear to be more frequent sequelae than hypothyroidism. The capacity for regeneration in thyroid glands of patients in this age group and the highly satisfactory response to thyroid in states of hypofunction recommend a more radical type of operation.

In 109 cases prepared for operation with iodine, Pemberton et al.[1] report a mortality of 2.8 per cent. Dinsmore [13] operated on 43 patients with two deaths after similar preparation.

Hyperthyroidism has been reported to occur in unusually early age groups. Warren and Shpiner [14] have reported primary hyperplasia of the thyroid gland in one of still-born twins from a mother who was five months pregnant and who aborted three days after a second partial thyroidectomy for moderately severe hyperthyroidism. White [15] has studied a fetus with primary hyperplasia of the thyroid gland whose mother was hyperthyroid, and Ochsner and Thompson [16] have observed this condition in an infant born of a hyperthyroid mother. Detailed reports have appeared on children five years of age and under with classical hyperthyroidism cured by subtotal thyroidectomy.[4, 6, 9, 17, 18]

Neff,[19] in 1932, reported twin sisters who developed hyperthyroidism at the age of eight and 10 years respectively. Fife [20] has recorded twin brothers who developed the disease at the age of 22 years. Careful search of the literature has not revealed the occurrence of the disease in dissimilar twins.

Case Report

This child was first admitted to the University Hospital on November 26, 1940 at the age of four years 11 months. His parents stated that for four weeks there had been nervousness and bulging of the eyes with polyphagia and the passage of three or four soft stools a day. In addition there had been enuresis two to three times nightly.

The child was born full term as one of dissimilar twins. A paternal aunt has a toxic goiter.

Physical examination revealed an overactive, irritable, talkative male child with a frequent brassy cough. The height was 43 inches and the weight 40 pounds. There was a marked degree of symmetrical exophthalmos with a pronounced lid lag and no wrinkling of the forehead on upward deviation of the eyes. He was unable completely to close his eyes. The skin was warm and moist with no eruptions. The thyroid

gland was diffusely enlarged and firm with a smooth, regular surface. A loud systolic bruit was heard over the entire gland, and the lower border of the gland could not be felt beneath the manubrium sternum. There was pronounced tremor of the outstretched hands and the tongue. There were enlarged, non-tender, discrete cervical, axillary and inguinal lymph nodes. The heart was normal in size and position, and the apex impulse was forceful with soft systolic mitral and aortic murmurs. The pulse rate was 122 per minute and the blood pressure 162 mm. Hg systolic and 40 mm. diastolic. The remainder of the examination was negative.

With the exophthalmometer at 92, a reading of 18 was obtained in each eye. There was a leukocytosis of 14,700 with 56 per cent small lymphocytes, and all other laboratory studies were within normal limits. A serum cholesterol was 182 milligrams per cent. A chest roentgenogram showed the heart to be globular in shape but normal

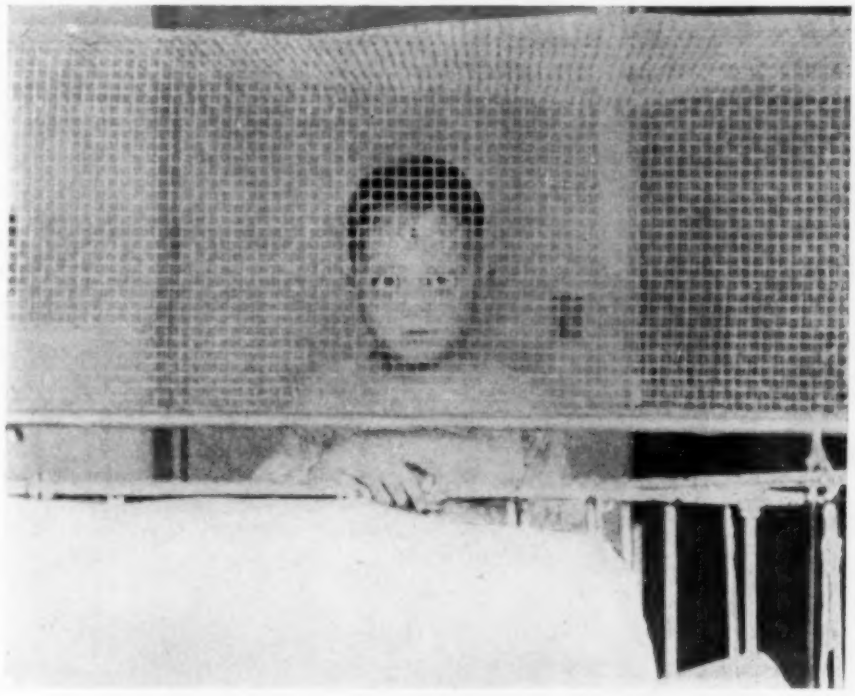

FIG. 1.

in size. There was no evidence of substernal thyroid, but there was an indefinite shadow suggesting a persistent thymus gland. Films of the extremities showed normal ossification, and the sella turcica was normal. An electrocardiogram showed a simple tachycardia with a rate of 107 per minute. There were no other significant changes. A basal metabolism test was attempted with the usual machine and was unsatisfactory.

The patient was placed on Lugol's solution, 10 drops three times a day, a high caloric, high vitamin diet and thiamin chloride, 5 milligrams twice a day. He was extremely restless and irritable, and it was impossible to maintain him as a bed patient. He roamed the hospital wards by day and night and, despite ordinary methods of restraint, was uncontrollable. He entered the premature nursery, seized an infant and after striking its head on the side of a wash basin, placed it under a running hot water

faucet. It was decided that more drastic means of control were required, and he was transferred from the pediatric to the medical service where an appropriate means of confinement had been prepared for him (figure 1). On December 19 a basal metabolic rate of plus 42 per cent was obtained following sedation with 2 grains of seconal.

During the first seven weeks of therapy the activation remained extreme, and the basal metabolic rate rose to plus 72 per cent. He developed a skin rash, nasal discharge and submaxillary gland enlargement, and accordingly the Lugol's solution was decreased to five drops a day. He received a short course of roentgen-ray therapy to the thymic region, and 12 weeks after the institution of iodine therapy the basal

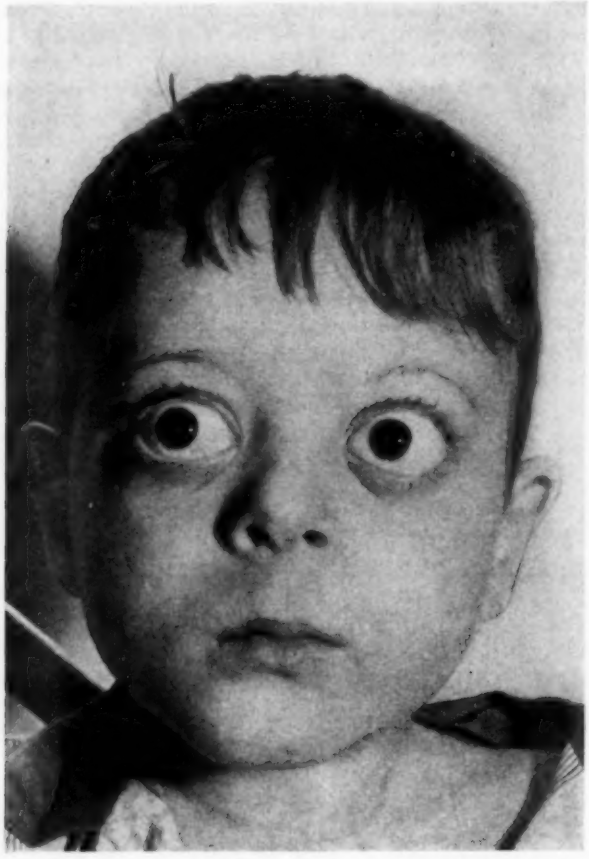

FIG. 2.

metabolic rate had fallen to plus 35 per cent and he had gained two and one-half pounds. On March 1, 1941 a right subtotal lobectomy with removal of the isthmus was performed under nitrous oxide and ether anesthesia. The 13 grams of tissue removed showed on section a hyperplastic gland with a slight degree of involution.

The postoperative course was complicated by the development of bilateral corneal ulcerations which healed rapidly without demonstrable scarring. Exophthalmometer readings showed a slight decrease in the degree of protrusion (figure 2). Iodine therapy with confinement was continued, and there was a decrease in the degree of activation. He developed uncomplicated rubella, and eight weeks after the first

operation the left lobe was removed, at which time the basal metabolic rate was plus 24 per cent. The pathological picture was identical with that reported for the previous tissue removed, and he was subsequently discharged from the hospital with a basal metabolic rate of plus 5 per cent.

Eleven months after discharge he was readmitted because of lassitude and increasing sensitivity to cold. Physical examination revealed a listless child with a pulse rate of 72 per minute and blood pressure of 104 mm. Hg systolic and 70 mm.

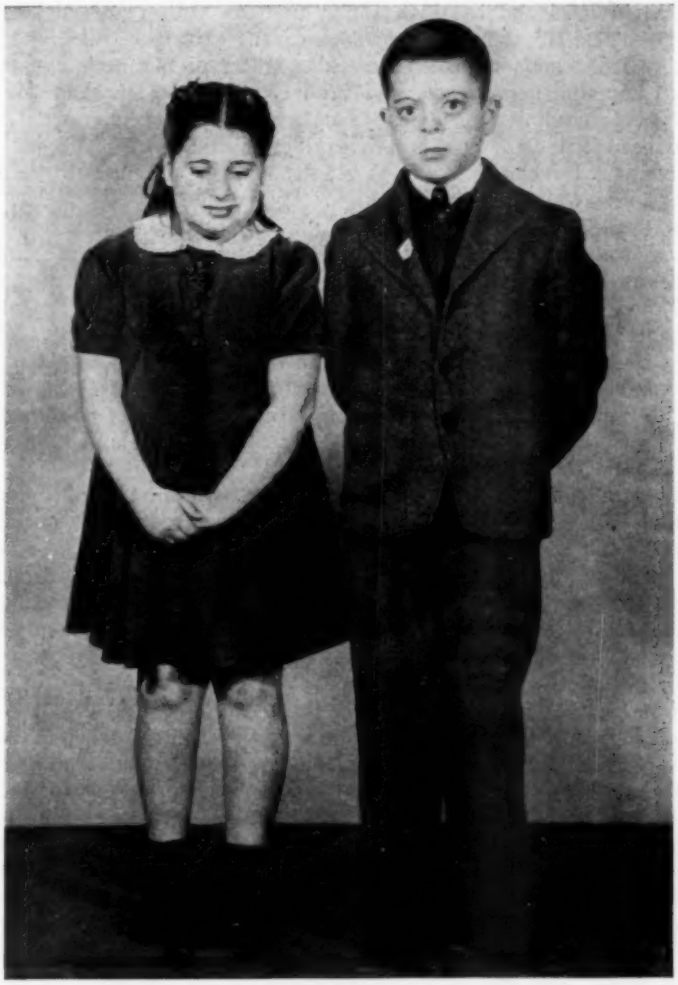

FIG. 3.

diastolic. His height had increased two inches and his weight 12 pounds since discharge. Although there was still a marked degree of exophthalmos, he was now able to close his eyes completely. There was no tremor and the skin was normal.

The basal metabolic rate was minus 36 per cent and the serum cholesterol 292 milligrams per cent. All other studies including an electrocardiogram were within normal limits. After one month of thyroid therapy, the basal metabolic rate had risen to minus 6 per cent, and there were no signs or symptoms of hypothyroidism.

Since discharge from the hospital, he has been maintained on ½ grain of thyroid daily and has developed as a normal child in all respects. At the age of 10 years he is in the fourth grade of school and has made satisfactory progress throughout his school years. He is not unusually emotional or talkative. There is still a moderate degree of exophthalmos which has not changed for three years (figure 3). There is no palpable thyroid tissue, and the heart sounds are soft with a rate on usual activity of 76 per minute and blood pressure of 104 mm. Hg systolic and 66 mm. diastolic. Height, span, lower measurement and weight are normal for his age. Urinary 17 ketosteroids, cholesterol and basal metabolic rate are within normal limits.

On October 10, 1943, the twin sister, age seven years 10 months, was admitted to the hospital. At five and one-half years enlargement of her neck had been noticed, and increased appetite, nervousness and failure to gain weight had soon appeared. Three months before admission her eyes had begun to bulge.

She had been delivered by a breech extraction and since birth had exhibited a spastic paraplegia. Development was slow; she had not talked until the age of three years, and had first walked at five years.

Physical examination revealed a moderate exophthalmos with lid lag, inability to converge, and absence of wrinkling of the forehead. The thyroid gland was symmetrically enlarged, firm and smooth with no bruit. The heart rate was 120 per minute, and there were no murmurs or enlargement. The blood pressure was 134 mm. Hg systolic and 66 mm. diastolic. There was a spastic paresis of the lower extremities. The basal metabolic rate was plus 49 per cent, and an electrocardiogram showed left ventricular strain with slight myocardial abnormality. Serum cholesterol was 191 milligrams per cent, and all other laboratory studies were within normal limits. Roentgenograms of the heart and lungs, long bones, and sella turcica were normal.

She was placed on a high caloric diet and sedated with 1 grain of phenobarbital a day. Shortly thereafter she developed an acute upper respiratory infection, and iodine therapy was, therefore, delayed until November 10, 1943 at which time all respiratory signs and symptoms had disappeared. She received 10 drops of Lugol's solution three times a day, and after 26 days of therapy the basal metabolic rate had fallen to plus 11 per cent, and she showed marked clinical improvement with a weight gain of 11 pounds. On December 16, 1943 a total thyroidectomy was performed under avertin and ether anesthesia. The postoperative course was uneventful, and she was discharged on December 23, 1943.

The pathological report described an intact thyroid gland in which no adenomata were seen. Microscopic examination revealed a hyperplastic gland with a slight degree of involution.

Three months after operation she was seen in the pediatrics dispensary because of increasing languor. Physical examination revealed a pulse rate of 60 per minute and blood pressure of 86 mm. Hg systolic and 48 mm. diastolic with no other stigmata of hypothyroidism. The basal metabolic rate was reported as minus 26 per cent, and she was placed on ½ grain of thyroid daily with subsequent improvement. However, she was readmitted to the hospital on August 4, 1944, seven and a half months after operation, at which time her parents complained of her fatigability and slowness in action, both mentally and physically. The basal metabolism rate of minus 8 per cent was obtained and the thyroid was increased to 1 grain a day with prompt improvement. Since that time her hypothyroidism has been completely controlled with thyroid. There is no residual exophthalmos and no palpable thyroid tissue. The heart rate on normal activity averages 70 per minute and the blood pressure 94 mm. Hg systolic and 62 mm. diastolic. She has remained moderately overweight and at 10 years of age weighs 78¼ pounds with a height of 129 cm., span 121.5 cm., and lower measurement 66 cm. The urinary excretion of 17 ketosteroids, blood cholesterol and basal metabolic rate are within normal limits.

Summary

A set of dissimilar twins in whom hyperthyroidism developed at the age of four years 10 months and seven years 10 months is reported. Following iodine therapy, subtotal thyroidectomy in multiple stages was performed in one patient, and a total thyroidectomy in the other. Postoperatively both patients manifested hypothyroidism which has been satisfactorily controlled with desiccated thyroid.

In the male child the degree of activation was extreme, necessitating confinement for the safety of himself and others.

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CIRRHOSIS OF THE LIVER ASSOCIATED WITH ALCOHOLISM; REPORT OF ACUTE EXACERBATION WITH SERIAL LIVER BIOPSIES *

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THE pathologic demonstration of the changes occurring during the course of cirrhosis of the liver has, until the recent revival of interest in liver biopsy, depended on the collection of single specimens of series of postmortem examinations or sporadic operations. Only rarely has there been available more than one observation on a given patient. Consequently, a series of liver biopsies obtained during a period of acute activity in a case of cirrhosis of the liver is of sufficient interest to justify reporting this case.

CASE REPORT

G. W. T., a 42 year old white highway engineer, was admitted to Touro Infirmary on April 2, 1946, with a chief complaint of jaundice. Fifteen years before admission, because of marital difficulties he began to drink from one-half to one pint of whiskey a day. He continued consuming large quantities of whiskey until 1941 when, following several weeks of increased drinking (one-fifth gallon a day), he noticed for the first time that his liver was enlarged. At that time there was dyspnea, nausea and vomiting but neither jaundice nor pain. He was told that he had some type of heart trouble. He discontinued drinking alcoholic beverages from this time until January 1946 and his liver decreased in size considerably but remained somewhat enlarged. Three months before admission to the hospital (January 1946), subsequent to a demand for more alimony from his divorced wife, he again began to consume large amounts of alcohol to the exclusion of eating. Three weeks before admission the liver was again noted to be enlarged and 10 days before admission jaundice was apparent. Three days before we saw him the feet, legs and abdomen began to swell gradually. Vomiting occurred on three occasions during the week before admission. There was nocturia (two times) with a history of dark urine for several days. The skin did not itch. The stools were light but not completely clay colored.

Physical Examination. The patient was a moderately obese, chronically ill, middle aged man lying propped up in bed. He was perspiring and moderately dyspneic. The blood pressure was 144 mm. Hg systolic and 74 mm. diastolic in both arms; the pulse rate was 140 beats per minute; the temperature was 100° F.; and the respiratory rate was 28 per minute. The skin, sclerae and mucous membranes were moderately icteric. The fundal vessels showed slight sclerosis. The heart was overactive but not definitely enlarged; the rate was 140 beats a minute and there was a gallop rhythm. Bilateral moist râles were heard posteriorly at the pulmonary bases. The diaphragms were high and the abdomen was moderately distended. There was an increase in collateral venous circulation, and shifting dullness in the flanks and a fluid wave were easily elicited. The liver was down 20 cm. below the right costal margin extending about 3 to 4 cm. below the umbilicus. The notch was easily palpable, and there seemed to be a large nodule immediately to the right of the notch. The spleen was not felt although examination was difficult because of distention and ascites. The feet, legs, abdominal wall and sacral region were considerably swollen.

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Laboratory Studies. On admission the venous pressure was 226 mm. of water in the right arm with rise to 270 on abdominal pressure. Arm to tongue circulation time was 10 seconds.

The urine was acid with a specific gravity of 1.005. The reactions for albumin and sugar were negative and positive for bile and urobilinogen. There were occasional finely granular casts and several epithelial cells on microscopic examination. The reaction to the serologic test for syphilis was negative. Bleeding time was three minutes and coagulation time two minutes. The hemoglobin was 83 per cent, red blood cell count 4,600,000, white blood cell count 18,800 (figure 1), neutrophiles 92

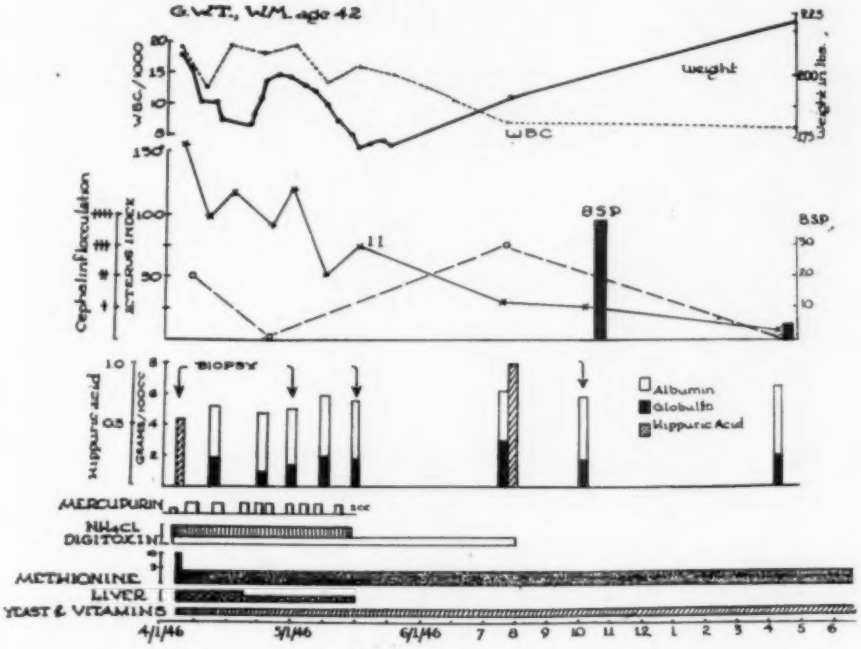

FIG. 1. Graphic representation of clinical course of G. W. T. from April 2, 1946 to June 1, 1947.

WBC—white blood count in thousands. ○ - - - ○—cephalin flocculation. BSP—Bromsulfalein retention test 5 mg./kg. 45 min. spec. Mercupurin—in 2 c.c. doses except the first. NH_4Cl—ammonium chloride 6 gm. per day. Digitoxin—1.2 mg. first day then 0.2 mg. per day. Methionine—10 gm. intravenously first day then 4 gm. day orally. Brewer's yeast—0.5 oz. three times day. Vitamins—1 Squibb therapeutic capsule a day. Hippuric acid—1.75 mg. sodium benzoate intravenously.

per cent, lymphocytes 8 per cent, prothrombin time 90 per cent of normal, cephalin flocculation 2 plus in 24 hours, non-protein nitrogen 27.1 mg. per cent, CO_2 combining power 50.4 mg. per cent, dextrose 97.5 mg. per cent, and icterus index 160.

An electrocardiogram showed definite evidence of myocardial disease. There was depression of the T-waves and ST segments in L I, II and CF_5. T_3 was inverted. A roentgenogram of the chest revealed cardiac enlargement with a transverse diameter of 15.8 cm., as well as chronic passive congestion of the pulmonary fields.

The patient was immediately digitalized with 1.2 mg. of digitoxin, and he was given 1 c.c. of mercupurin intravenously.

Liver biopsy done with a Roth-Turkel needle [1] on April 5, 1946 revealed indistinct lobules, the cell cords showing extensive large and small fat droplets, cellular de-

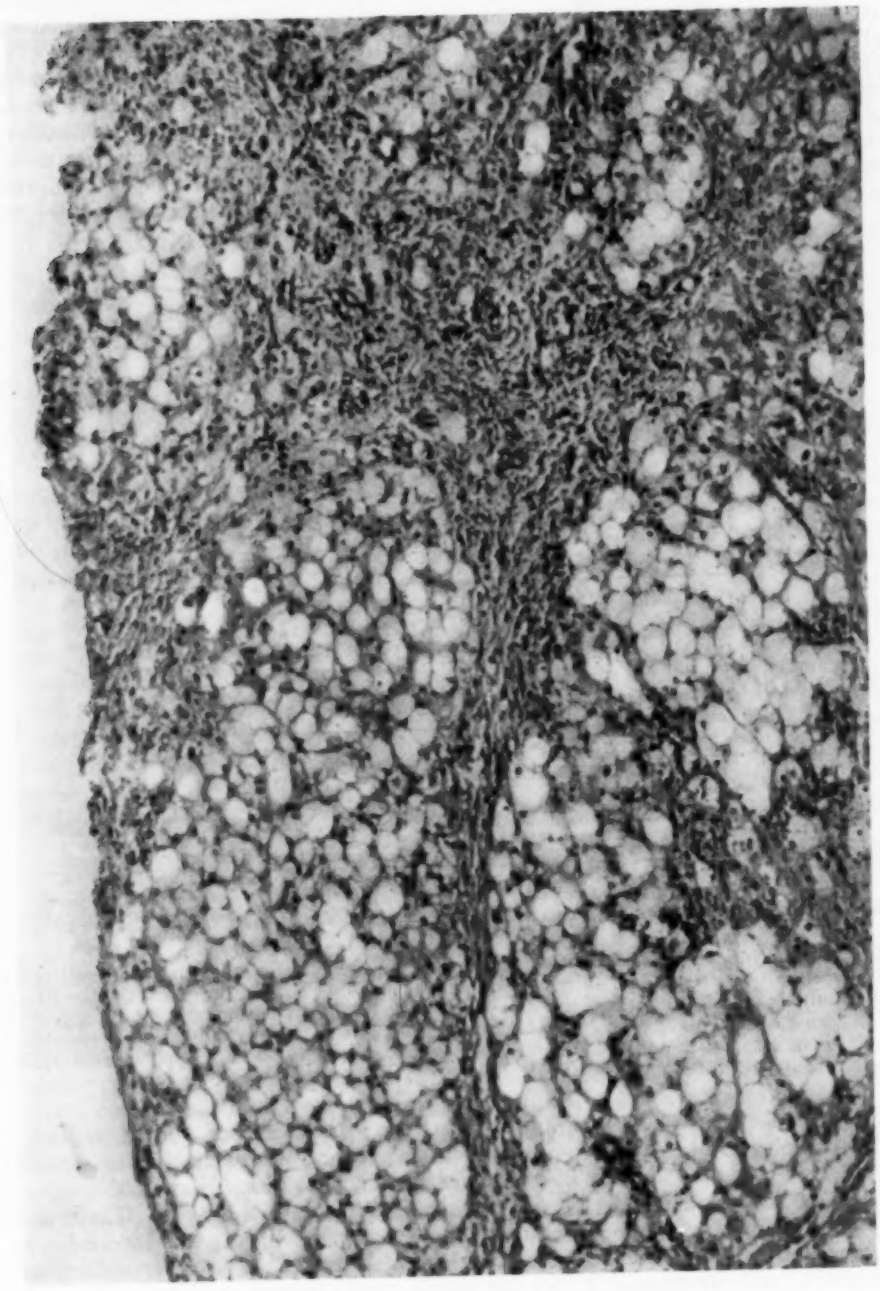

FIG. 2a. Photomicrograph (April 4, 1946) showing perilobular and intralobular fibrosis with diffuse fatty change, degeneration and neutrophilic infiltration. Moderate bile duct proliferation can be seen in the portal areas. ×80.

FIG. 2*a*. Photomicrograph (April 4, 1946) showing perilobular and intralobular fibrosis with diffuse fatty change, degeneration and neutrophilic infiltration. Moderate bile duct proliferation can be seen in the portal areas. × 80.

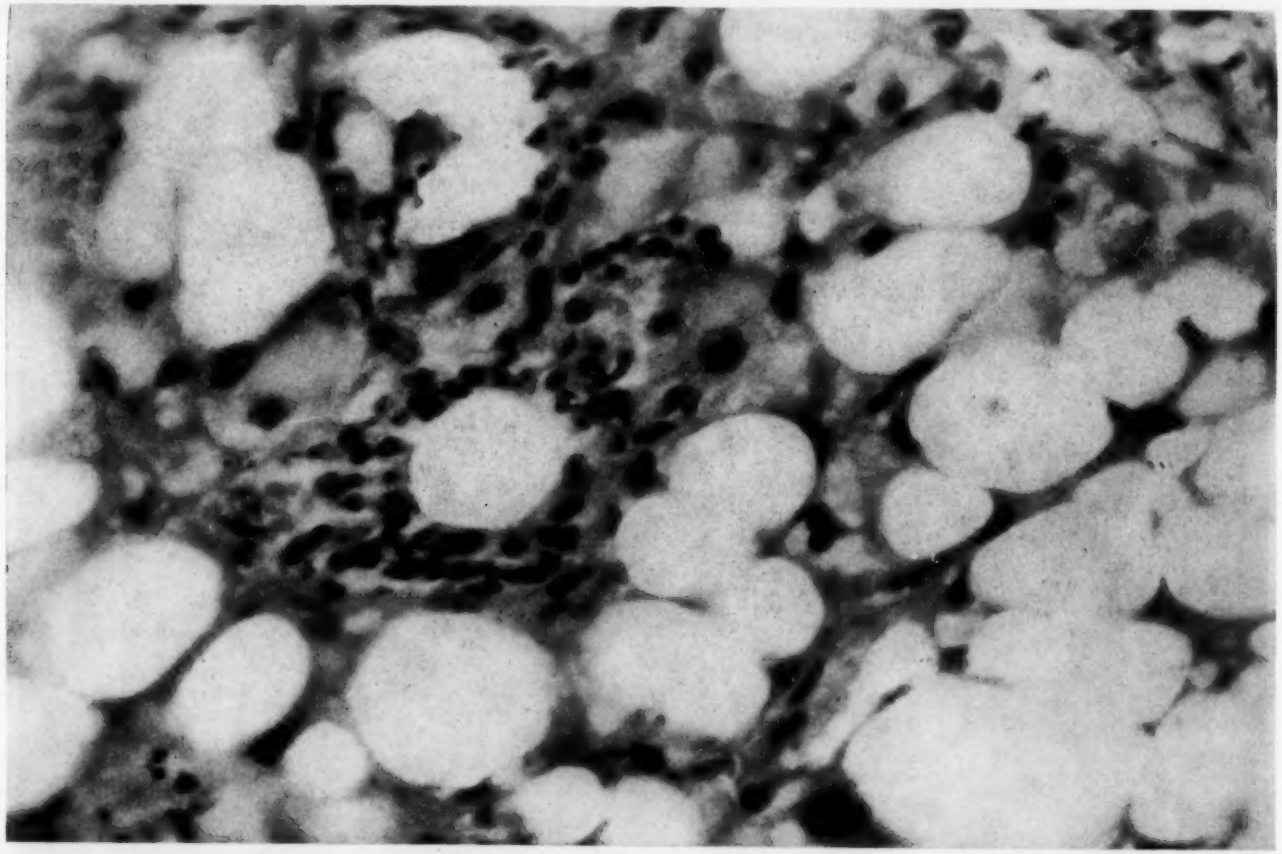

FIG. 2*b*. Photomicrograph (April 4, 1946) showing intralobular collections of polymorphonuclear leukocytes with cellular degeneration and fatty change. × 400.

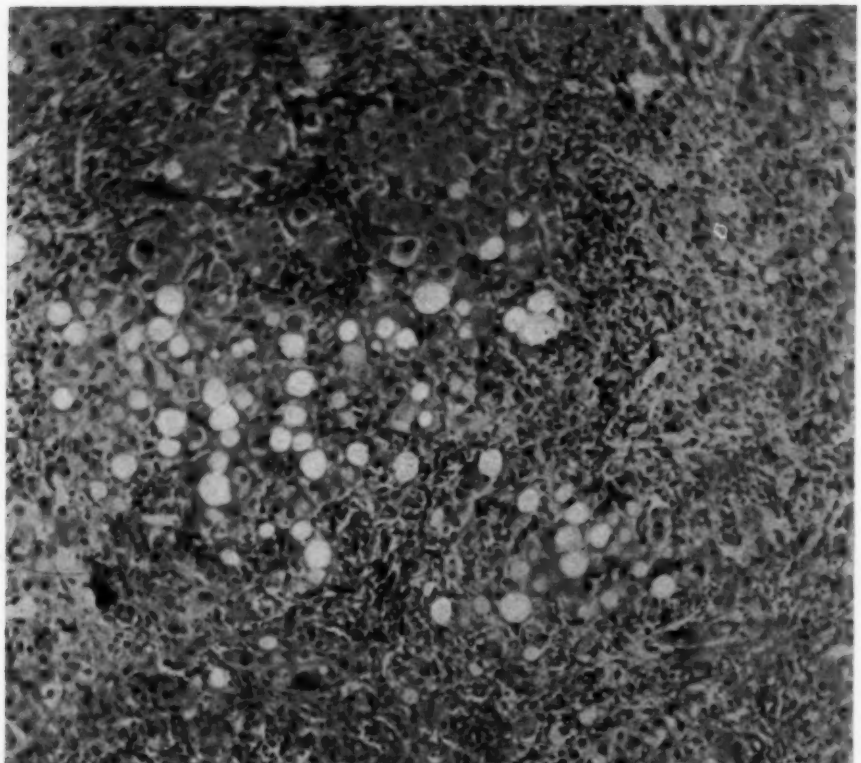

FIG. 3a. Photomicrograph (April 30, 1946) showing decrease in hepatic cellular degeneration and fatty change with increase in glycogen storage. Evidence of regeneration in binucleated liver cells. Neutrophilic infiltration still prominent, though increased numbers of round cells are beginning to appear. × 80.

generation and diffuse neutrophilic infiltration (figure 2). Biliary thrombi were not infrequently seen, and there was considerable portal fibrosis with proliferation of biliary radicals. The microscopic diagnosis * was "portal cirrhosis, severe; fatty degeneration of the liver, severe; acute parenchymatous degeneration with neutrophilic response."

Hospital Course. The patient was given methionine ‡ (10 gm.) intravenously and started on a diet of carbohydrate (500 grams) and protein (200 grams) with no fat added. Methionine (1 gm.) was given four times a day by mouth, brewer's yeast (0.5 oz.) three times a day, crude liver extract 5 c.c. intramuscularly daily for five days and then three times a week.

On April 8, 1946 the white blood count was 13,050, neutrophiles 90 per cent, lymphocytes 7, eosinophiles 3, icterus index 100. On April 9, 1946 the hippuric acid excretion test with 1.77 gm. of sodium benzoate given intravenously yielded 0.535 gm. of hippuric acid in one hour in the urine. On April 11 the total serum protein was 5.17 gm. per 100 c.c., serum albumin 3.3 gm. per 100 c.c., serum globulin 1.87 gm. per 100 c.c. On April 12 the white blood cell count was 19,350, neutrophiles 90 per cent, lymphocytes 8, eosinophiles 1, monocytes 1. On April 13 the icterus index was 120. On April 15 the electrocardiogram showed no change from the previous one. On this date the white blood cell count was 17,750, neutrophiles 84 per cent, lymphocytes 13, eosinophiles 3, prothrombin time 60 per cent, non-protein nitrogen 27, icterus index 90, total serum protein 4.66 gm. per 100 c.c., serum albumin 3.66 gm. per 100 c.c., serum globulin 1.00 gm. per 100 c.c. On April 16 the prothrombin time was 48 per cent of normal as a consequence of which menadione was started parenterally.

The patient's condition remained essentially the same until April 17, 1946, when 600 c.c. of clear, bile-stained fluid were removed by paracentesis, following which the spleen was felt about 6 cm. below the left costal margin. Mercupurin was given about three times a week and the edema gradually cleared. Venous pressure on April 25, 1946 was 150 mm. of water increasing to 290 on liver pressure with arm-to-tongue circulation time 13 seconds. On April 29, 1946, the white blood cell count was 18,450, neutrophiles 87 per cent, lymphocytes 8, eosinophiles 2, monocytes 1, prothrombin 78 per cent, non-protein nitrogen 27, icterus index 120, total serum protein 4.99 gm. per 100 c.c., serum albumin 3.30 gm. per 100 c.c., serum globulin 1.49 gm. per 100 c.c.

Biopsy repeated on April 30, 1946 (figure 3) revealed accentuation of all the features seen in the first biopsy with the exception of fatty metamorphosis which was moderately reduced in this specimen. From the appearance of the biopsy, the liver reserve was considerably diminished. The diagnosis was "portal cirrhosis, severe; fatty degeneration of liver, severe; acute parenchymatous degeneration with neutrophilic response." The glycogen storage in this specimen was much more in evidence than in the previous one and the neutrophilic infiltration was, in general, lessening. Eosinophilic and round cell infiltration was beginning to be noticeable. On May 6 the white blood cell count was 13,700, prothrombin time 90 per cent, non-protein nitrogen 26 mg. per cent, icterus index 50, total serum protein 5.85 gm. per 100 c.c., serum albumin 3.85 gm. per 100 c.c., serum globulin 2.00 gm. per 100 c.c. On May 13 the white blood cell count was 16,350, the prothrombin time was 90 per cent, total serum protein 5.48 gm. per 100 c.c., serum albumin 3.68 gm. per 100 c.c., serum globulin 1.80 gm. per 100 c.c. The venous pressure was 110 mm. of water increasing to 118 mm. of water on liver pressure with circulation time 14 seconds.

A roentgenogram of the chest showed clear lungs and a normal heart measuring 13.1 cm. (2.7 cm. decrease). The electrocardiogram showed definite improvement in that the T-waves were normal and the ST segments were only slightly depressed.

* Made by Dr. S. Harvey Colvin, Touro Infirmary Pathologist, for whose advice and suggestions we are extremely grateful.

‡ Kindly made available by Wyeth, Inc.

FIG. 3a. Photomicrograph (April 30, 1946) showing decrease in hepatic cellular degeneration and fatty change with increase in glycogen storage. Evidence of regeneration in binucleated liver cells. Neutrophilic infiltration still prominent, though increased numbers of round cells are beginning to appear. × 80.

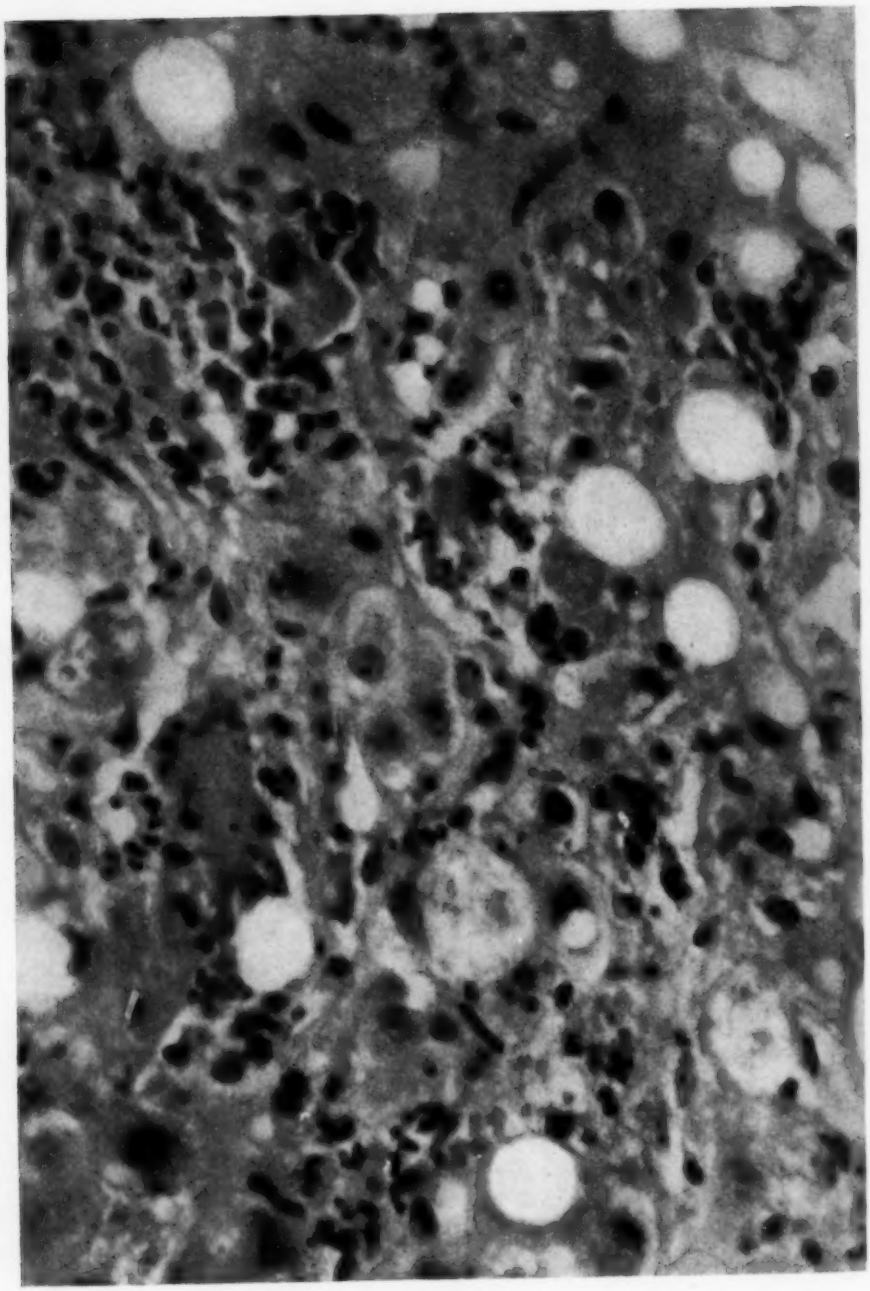

FIG. 3b. Photomicrograph showing increased glycogen storage in liver cells with moderate fatty change and marked neutrophilic infiltration. Note smudges of hyaline degeneration of liver cells in these areas. × 400.

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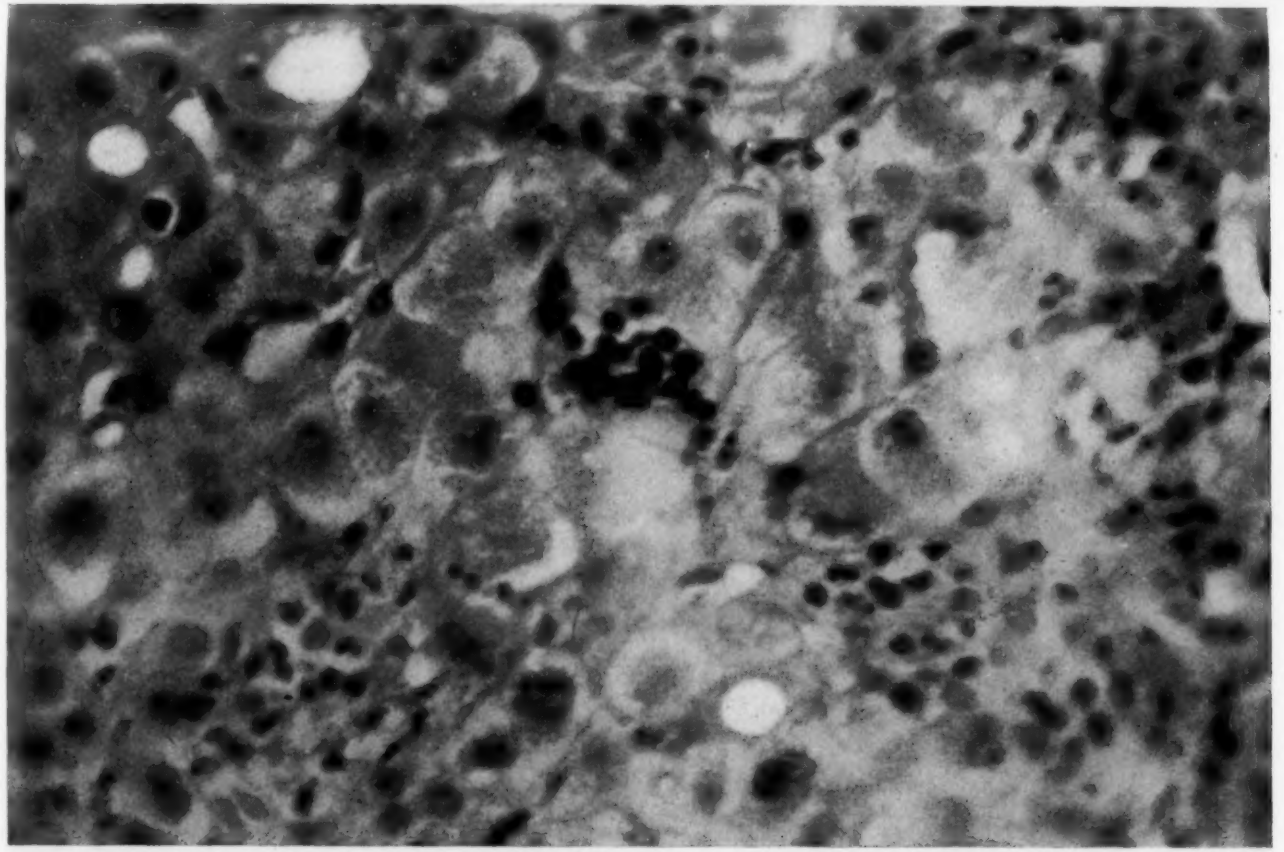

FIG. 3c. Photomicrograph showing a collection of round cells in intralobular situation. × 400.

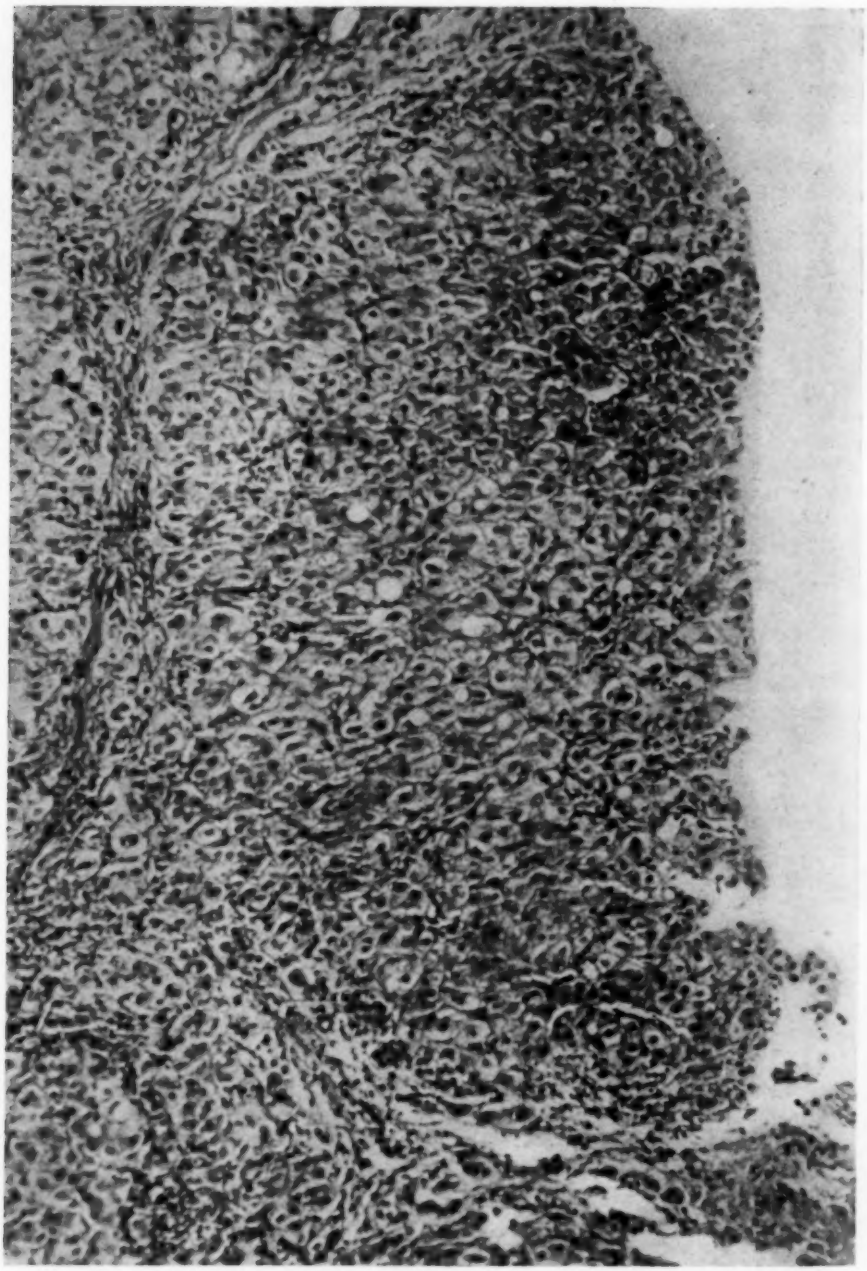

FIG. 4a. Photomicrograph (May 14, 1946) showing little remaining fatty change and moderate cellular infiltration chiefly of round cell type. Marked glycogen storage is seen. × 80.

FIG. 4*a*. Photomicrograph (May 14, 1946) showing little remaining fatty change and moderate cellular infiltration chiefly of round cell type. Marked glycogen storage is seen. × 80.

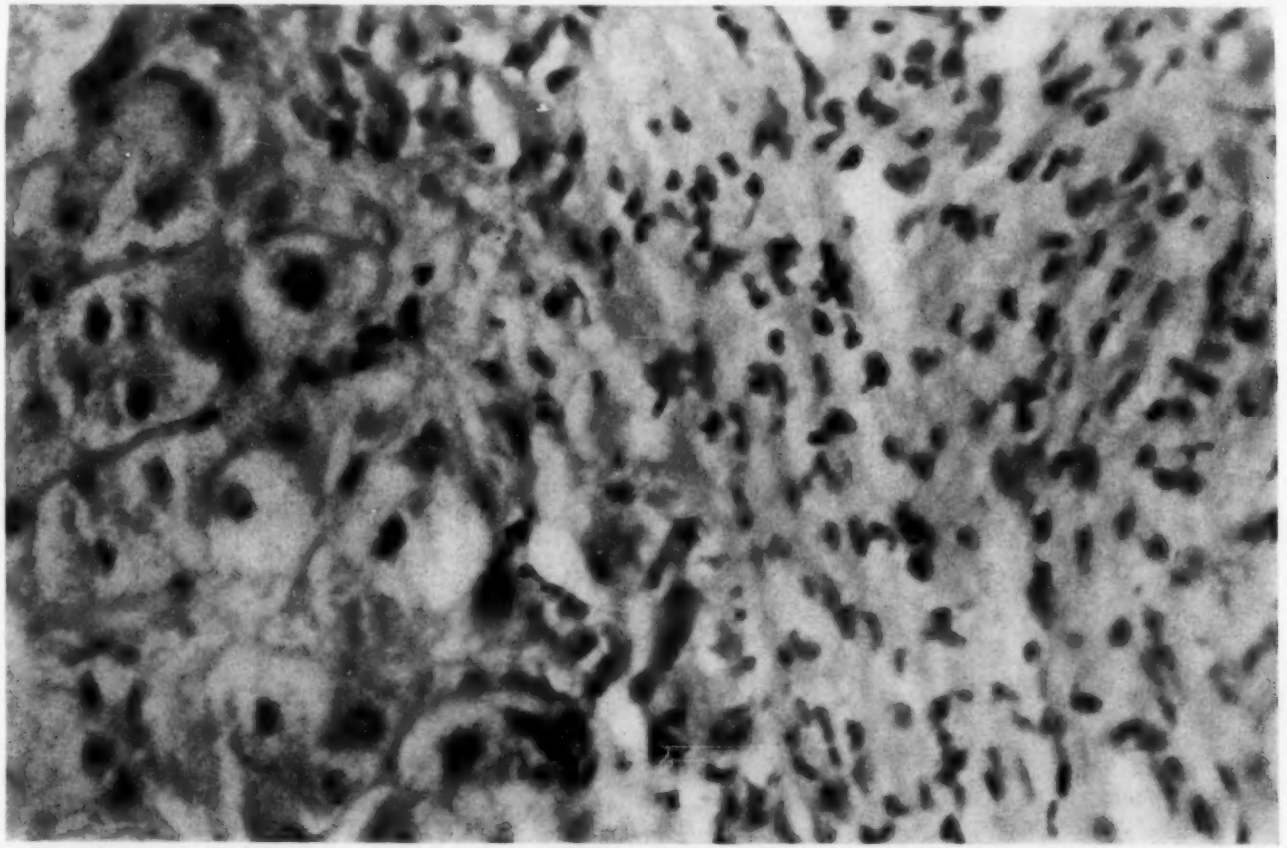

FIG. 4*b*. Photomicrograph showing remaining parenchymal and fibrous tissue cellular infiltrate chiefly round cell in nature. × 400.

The congestive failure had completely subsided by May 13, 1946, and the patient was feeling a great deal better.

In the third biopsy on May 14, 1946 (figure 4) microscopic examination revealed that the lobules were made up primarily of large glycogen-filled granular appearing cell cords surrounded by moderate amounts of connective tissue infiltrated with round cells. Several lobules contained foci of infiltration with large fat droplets and focal collection of neutrophiles. Biliary thrombi were occasionally noted as in the previous biopsies. The greater part of the cellular infiltration, however, was made up of round cells. This biopsy suggested that the liver reserve, though still considerably diminished, was better than in previous biopsies. The diagnosis was severe portal cirrhosis, slight fatty degeneration of the liver, and acute parenchymatous degeneration with mild neutrophilic response. There was also considerable evidence of regeneration both of bile ducts and hepatic parenchyma.

The patient adhered rigidly to his diet though he had a rather severe degree of anorexia. He had a low grade fever (99.5° F.) during most of his hospital stay.

The patient was discharged from the hospital on May 17, 1946. He continued his therapeutic regimen at home with minimal physical activity, methionine, brewer's yeast, vitamins * and diet as before. He returned on July 17, 1946 looking and feeling well. His weight had increased from 175 to 190 pounds, which represented largely muscle. There was no visible icterus. The blood pressure was 140 mm. Hg systolic and 80 mm. diastolic in the right arm in the supine position. The chest was clear, the heart not enlarged, and the rate 90 per minute, with regular sinus rhythm. Soft systolic, pulmonic and mitral murmurs were heard. The abdomen was relaxed, the liver was down only 3 cm. below the right costal margin and the spleen 4 to 5 cm. There was minimal edema of the ankles.

Laboratory studies at this time revealed the following: total serum protein 6.2 gm. per 100 c.c. with albumin 3.2 gm. per 100 c.c. and globulin 3.0 gm. per 100 c.c., non-protein nitrogen 20 mg. per cent, bilirubin 2.8 mg. per cent, hippuric acid excretion 1.0 gm., sedimentation rate 3 mm. per hour, red blood cell count 4,100,000, hemoglobin 80.5 per cent, white blood cell count 7,500, polymorphonuclears 64 per cent, lymphocytes 27, monocytes 5 and eosinophiles 4.

The patient was again discharged with instructions to follow the previous regimen. He returned October 5, 1946 feeling well and working full time with an hour's rest in the middle of the day. There was absolutely no evidence of heart disease, ascites or edema. Blood pressure was 130 mm. Hg systolic and 75 mm. diastolic in the right arm. The chest was clear. The heart was not enlarged, the rate 80 per minute, rhythm regular sinus with an occasional ectopic beat and no murmur. The abdomen was relaxed. The liver, which was down 2 cm. below the right costal margin, was firm, smooth and nontender. It descended to 6 cm. on deep inspiration and the spleen descended only 2 cm.

Another liver biopsy was done on October 7, 1946 (figure 5). Sections revealed numerous islands of glycogen-filled cell cords surrounded by considerable amounts of fibrous connective tissue. There was moderate biliary radical proliferation. The diagnosis was portal cirrhosis of the liver. The glycogen content was notably increased and the fat was absent. Cellular infiltration had completely disappeared and there was no evidence of degeneration at this time.

Laboratory studies revealed total serum protein 5.8 gm. per 100 c.c., serum albumin 4.1 gm. per 100 c.c., serum globulin 1.7 gm. per 100 c.c., non-protein nitrogen 22 mg. per cent, bilirubin 2.64 mg. per cent, bromsulfalein excretion test, 37 per cent retention at 60 minutes, sedimentation rate 1 mm. per hour, red blood cell count 4,480,000, hemoglobin 14.5 gm. per cent, white blood cell count 7,350, neutrophiles 47 per cent, lymphocytes 37, monocytes 6, eosinophiles 8, basophiles 2, cephalin floccula-

* Squibb therapeutic.

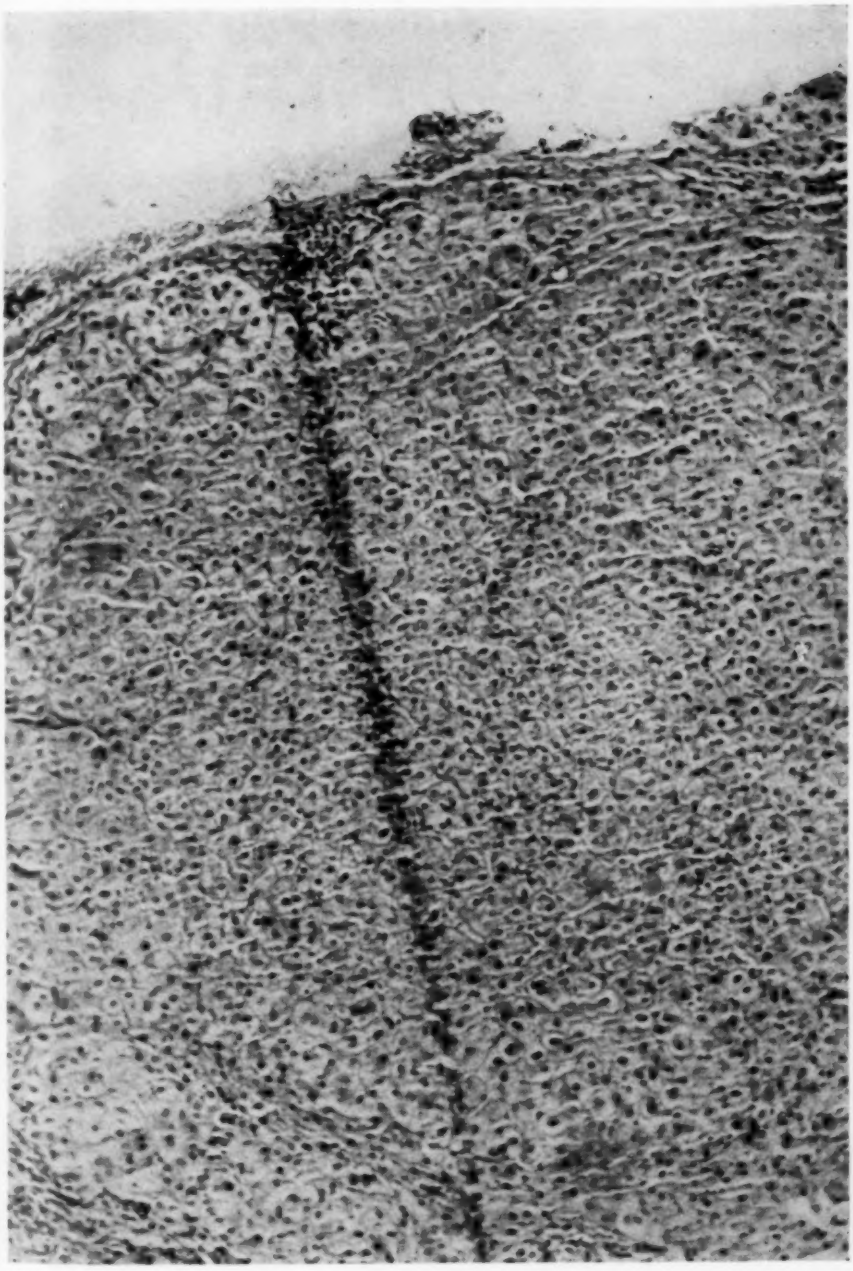

FIG. 5a. Photomicrograph (October 7, 1946) showing complete absence of fatty change and cellular infiltration. There is marked glycogen storage and still some evidence of regeneration of liver tissue. × 80.

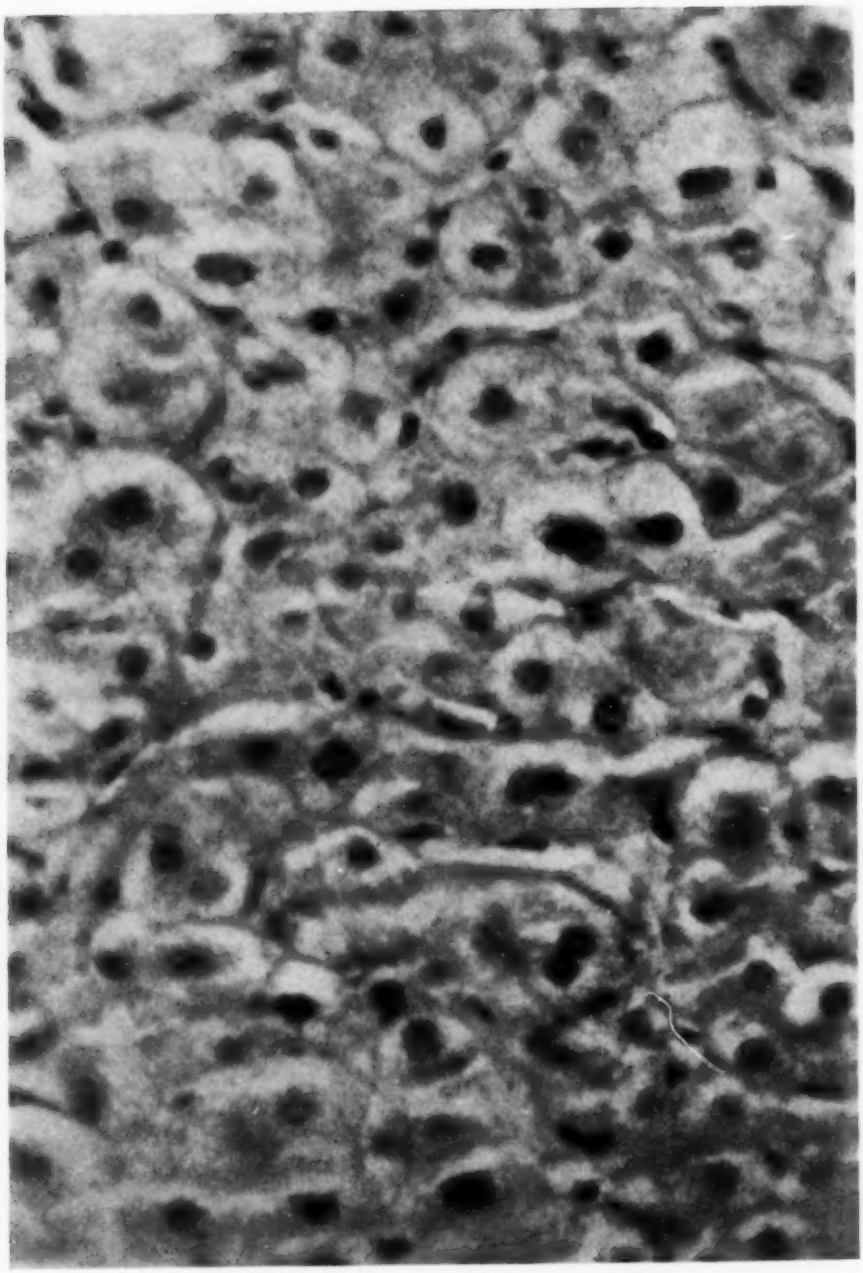

FIG. 5*b*. Photomicrograph showing glycogen filled liver cells—several with two nuclei and no cellular infiltration. × 400.

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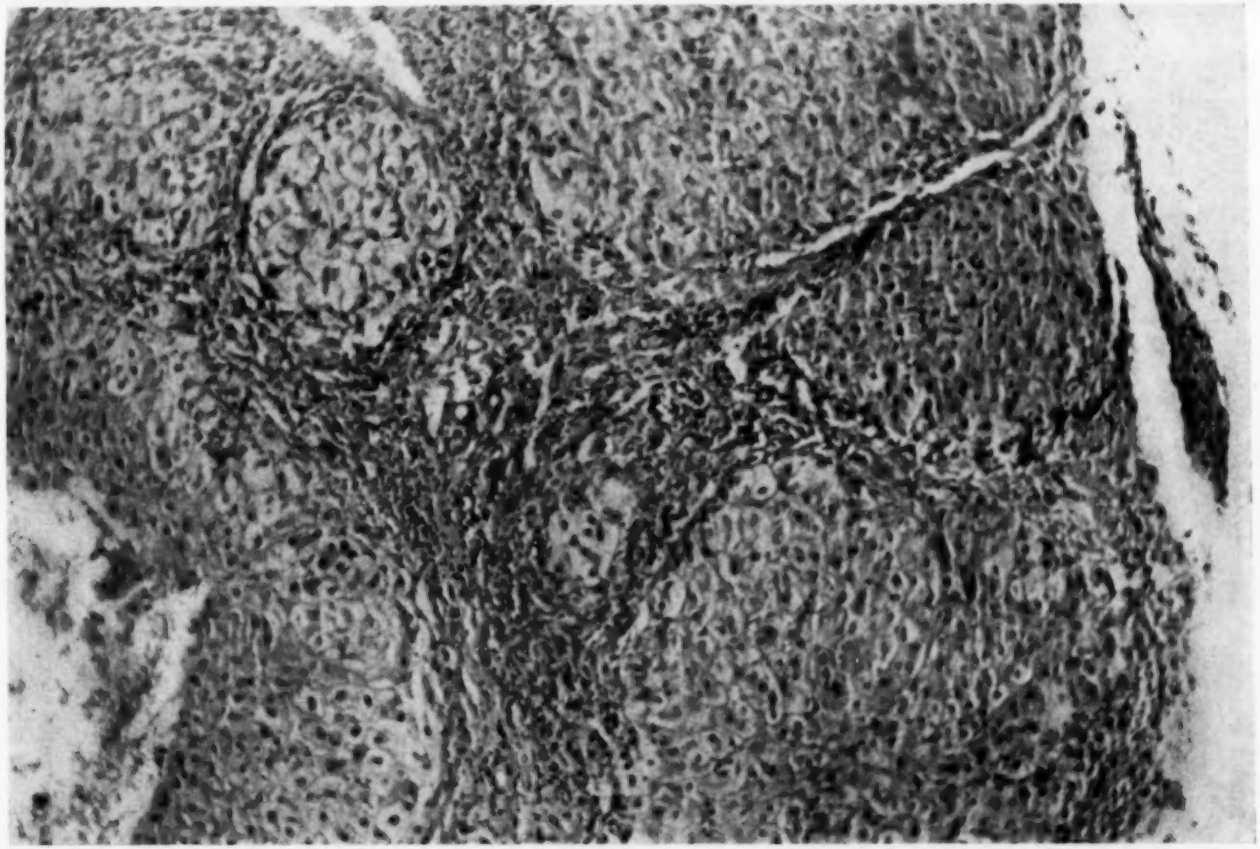

FIG. 5*c*. Photomicrograph showing another area from the same slide to illustrate variation in fibrosis in different areas of the liver. × 80.

tion test 3 plus, prothrombin time 116 per cent. The reaction to the test for bile in the urine was negative, for urobilinogen positive in dilution of 1:20.

The patient was again discharged; he was permitted to work full time and told to continue with his diet, methionine and vitamins. He returned on April 12, 1947 feeling perfectly well, working full time but still taking no strenuous exercise. He weighed 222 pounds at this time. The blood pressure in the right arm was 140 mm. Hg systolic and 85 mm. diastolic. The fundi were normal; there was no trace of icterus; the chest was clear and the heart normal. The abdomen showed no evidence of increased collateral circulation; the liver still descended 5 to 6 cm. below the right costal margin on deep inspiration and was firm and nontender; the spleen was about half its size on the previous visit, coming down 1 to 2 cm. on deep inspiration. There was no edema.

Laboratory studies at this time were as follows: red blood cell count 5,200,000, hemoglobin 94 per cent, while blood cell count 6,900, neutrophiles 47 per cent, lymphocytes 52, eosinophile 1, urine urobilinogen excretion 0.96 Ehrlich unit for two hour period, total serum protein 6.4 gm. per 100 c.c., serum albumin 4.3 gm. per 100 c.c., serum globulin 2.1 gm. per 100 c.c., non-protein nitrogen 24 mg. per cent, bilirubin 1.09 mg. per cent, bromsulfalein 5 per cent retention (at 45 minutes); the cephalin flocculation test yielded negative results. The patient had had absolutely no alcohol since his admission to the hospital April 2, 1946.

Discussion

The etiology of the cirrhosis in this case seems clearly related to a combination of dietary deficiency and inordinate use of alcoholic beverages. There was no history of blood transfusion, plasma infusion, vaccination, antisyphilitic therapy or other exposure to the virus of hepatitis or chemical hepatotoxin, and no evidence of biliary obstruction. The clinical course of the episode is shown graphically in figure 1. Of particular interest are the presence of persistent, severe, congestive heart failure with electrocardiographic changes which cleared completely as the hepatic disease regressed, close agreement between the fluctuations in icterus index and white blood cell count, a good response to prolonged hyperalimentation, the administration of methionine, brewer's yeast, liver extract and supplementary vitamins, and the laboratory evidences of prolonged hepatic dysfunction after clinical improvement. The low initial value of the cephalin flocculation test and its subsequent increase after other evidences of activity were subsiding is difficult to explain. From the chart it may be seen that there was fairly good inverse correlation with the albumin/globulin ratio.

The presence of congestive heart failure in association with cirrhosis of the liver and ascites has been clinically recognized for many years.[2, 2a] The actual mechanism in the case just described is questionable. The absence of hypertension and valvular defects, and the presence of transient electrocardiographic changes, gain in weight and normal pulse pressure rule out the common causes of heart disease and leave for consideration toxic myocarditis and heart failure due to thiamine deficiency. The fact that there was no concomitant evidence of severe vitamin deficiency mediates against the diagnosis of beriberi heart. The reversible electrocardiographic changes, the roentgenologic decrease in the size of the heart, and the disappearance of congestive failure with control of the hepatic dysfunction favor interpretation of myocardial insufficiency as secondary to the hepatic disease. The pronounced hepatomegaly and ascites were probably related to the combination of hepatic difficulty and cardiac insufficiency whereas the change in size of the liver was related to the reëstablishment of myocardial

competency as well as to the disappearance of fatty infiltration and inflammatory reaction. Persistent leukocytosis and low grade fever in association with fatty liver and "alcoholic cirrhosis" have been mentioned by Keefer and Fries,[3] Hall and Morgan,[4] and Davis,[2, 2a] though the cause is not clear. In the present case there was good agreement between peripheral leukocytosis and neutrophilic response in the liver.

Microscopically, of particular interest in the initial biopsy is the severe degree of fatty change, liver cell degeneration and pronounced generalized polymorphonuclear leukocytic infiltration throughout the lobules as well as in the periportal connective tissue (figure 2). Fibrous tissue is present in moderate amount though less noticeable because of the considerable crowding of the fat. Bile duct regeneration and biliary thrombi are present though not particularly noticeable in the first biopsy specimen. Fatty change in the liver is well known in cirrhosis and was first noted by Addison.[5] It has been repeatedly mentioned as the cause of "alcoholic cirrhosis."[2, 4, 6, 7] Discussion of the validity of this contention is not pertinent at this time.

Although the polymorphonuclear leukocytic infiltration has been described previously,[1, 4, 7, 8, 9, 10] extensive diffuse infiltration is apparently not common and there has been relatively little emphasis on its occurrence in the past few years. The significance of neutrophilic infiltration is obscure. It has been suggested that such change is in response to ascending bacterial or chemical cholangitis, but in such an instance the change should be localized to the peribiliary areas and this was not the case. Neutrophilic response to cellular degeneration is a well known pathologic phenomenon, but again the specific reason for its appearance in some situations and absence in others is not clear. For example, in the severe cellular degeneration of epidemic hepatitis,[11, 12, 13] acute yellow atrophy,[14] yellow fever [15] and related conditions, neutrophilic infiltration, though present in some instances, is not great and the predominating cells are usually round cells. It is believed that the presence of such diffuse neutrophilic infiltration may have diagnostic significance in acute degenerative change associated with alcoholism and malnutrition. It is apparently not associated with the fatty infiltration of the liver in pellagra.[16] The specific factor responsible remains to be identified.

Subsequent biopsies in the case reported showed gradual disappearance first of the fatty degeneration with replacement by glycogen, and later disappearance of the polymorphonuclear leukocytes and replacement by round cells, with accentuation of the biliary radicals and increase in perilobular and intralobular fibrosis. This is probably a relative rather than an absolute change depending on the disappearance of fatty infiltration. In the last biopsy there remained only the picture of quiescent cirrhosis. It is, of course, impossible to assess accurately the place of methionine in the therapeutic response of this patient because of the lack of control observations. The clinical impression is, however, that it was of considerable value. Of undoubted benefit was the determined coöperation of the patient in eating all his diet during the whole course of illness.

Summary

We have presented a case of cirrhosis of the liver showing an acute exacerbation associated with alcoholism with serial liver biopsies. The series shows

resolution of the severe fatty degeneration and polymorphonuclear infiltration over a period of six months closely paralleling the clinical and laboratory evidences of improvement. Remarkable features included the presence of severe congestive heart failure which disappeared spontaneously with the resolution of the hepatic lesions, low grade fever, leukocytosis, and polymorphonuclear leukocytic infiltration of the liver which also resolved. It is noteworthy that the result of the cephalin cholesterol flocculation test did not follow closely the microscopic and other laboratory evidence of hepatic damage other than the albumin/globulin ratio.

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RELAPSING FEBRILE NODULAR NONSUPPURATIVE PANNICULITIS: REPORT OF CASE TREATED WITH PENICILLIN *

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Relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian's disease) is a rare clinical syndrome which was first described by Pfeiffer [1] in

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1892. Subsequent reports, including one by Weber [2] who added the word febrile to the name, brought the number of cases known at present to 29.

As the name implies, this is a chronic recurrent condition, characterized by attacks of fever associated with nonsuppurating nodules in the subcutaneous fatty tissue. The most common localization is in the lower extremities, and of the 29 cases reported in the literature, 24 have been found in women and only five in men.

The condition occurs in repeated attacks, each of which may last up to several months with spontaneous remissions. There is usually generalized malaise of varying degree. Only one case with a fatal outcome has been reported. The nodules, which are the characteristic feature of this syndrome, vary in size from 0.5 cm. to 5 cm. in diameter. They are usually tender, and the overlying skin has a blue, livid discoloration and shows a definite depression when the nodules undergo involution.

The etiology of relapsing febrile nodular nonsuppurative panniculitis is unknown. However, most observers agree that the halogens (bromides, chlorides, and iodides) may be of etiological significance. In the majority of cases there is definite history of halogen ingestion, and Rosenberg and Cohen [3] cite a case in which they were able to precipitate a recurrence by giving the patient bromides and chlorides.

No specific treatment is known and therapy has been merely symptomatic. Arnold [4] reports a case which responded favorably to sulfapyridine, whereas other observers agree that the sulfonamides are of no benefit. We have not found any reports of cases in which penicillin was used.

In view of the rarity of the condition and the lack of knowledge of its etiology and therapy, we believe that the report of an additional case is justified, particularly since this appears to be the first case treated with penicillin.

Case Report

History. The patient, a white female, 35 years of age, was admitted to the hospital on September 17, 1946, complaining of hoarseness, sore throat, and lumps in the right calf below the knee.

She had first become ill in January, 1945, when she began feeling tired and noticed pain under the right shoulder blade. She became hoarse and had noticed intermittent hoarseness since that time. In September 1945 she developed fever and headache, and her face became very swollen. These symptoms subsided, but in July 1946 the swelling of the face and the headache recurred, and she developed a sore throat. She had one chill at the time. She then developed several nodules in her right calf. These were not painful, but they burned and caused what she called a "creepy feeling." She had lost 14 pounds in weight during a period of a few months prior to admission, and she had developed several ulcers in her mouth. These ulcers healed but recurred in a few days. Two weeks prior to admission the outer angle of her right eye became sore with swelling of both lids.

The patient stated that she worked as a clerk in a drug store and that she had been taking a great deal of medicine. When asked to write down the drugs she had been taking, she produced the following list from memory: Salts, Vick's Nose Drops, Prothricin Nose Drops, Viburnum plus HVC, Migraine Tablets, P. A. C. Tablets, Mineral Oil, Benadryl Capsules, Kaopectate, a bismuth and magnesium mixture, Sulfathiazole, Aspirin, Cold Capsules, Rexall Kidney Pills, bromoseltzer (about two doses), thyroid tablets, a large blue kidney pill, Menthol Blue, a tonic for

appetite, multiple vitamins, vitamin D pills, and ovarian shots. She had also been using iodized salt for kitchen and table use.

Physical Examination. The patient was a white female weighing 118 pounds, who appeared chronically ill. Her blood pressure was 100 mm. Hg systolic and 68 mm. diastolic, temperature 98.2° F., pulse 76, and respirations were 20. There was moderate inflammation of the outer canthus of the right eye with a small fissure,

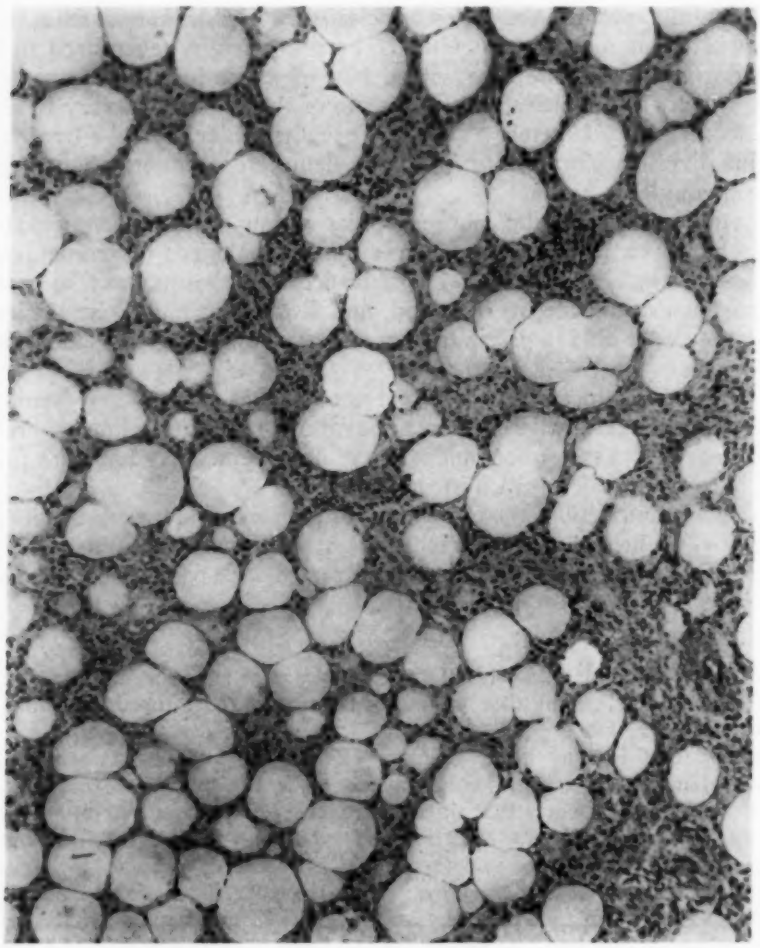

FIG. 1. Low power photomicrograph (× 125) showing the characteristic appearance of the lesion.

and diffuse edema of the eyelids and adjacent tissue. The pharynx showed a vertical ulcer 5 by 3 mm. on the left posterior wall within a red, swollen area. The base of the ulcer was covered with white-yellow mucus. The edges were sharp and slightly indurated but not undermined. The mucous membrane of the larynx was edematous. Several enlarged, submandibular lymph nodes were noted bilaterally.

Numerous discrete, subcutaneous nodules, measuring 5 to 20 mm. in diameter, were found in the right calf in an area extending from a point 5 cm. below the knee

to a point 5 cm. above the Achilles tendon. The nodules were not tender and were freely movable. The overlying skin was livid.

Laboratory Studies. Roentgen-ray of the chest was negative. Urinalysis was negative. The red blood cell count was 4,060,000 with a hemoglobin of 12 gm. (Haden-Hausser). The white blood cell count was 5,500. The differential count showed 79 per cent segmented neutrophiles, 19 lymphocytes, 1 monocyte, and 1

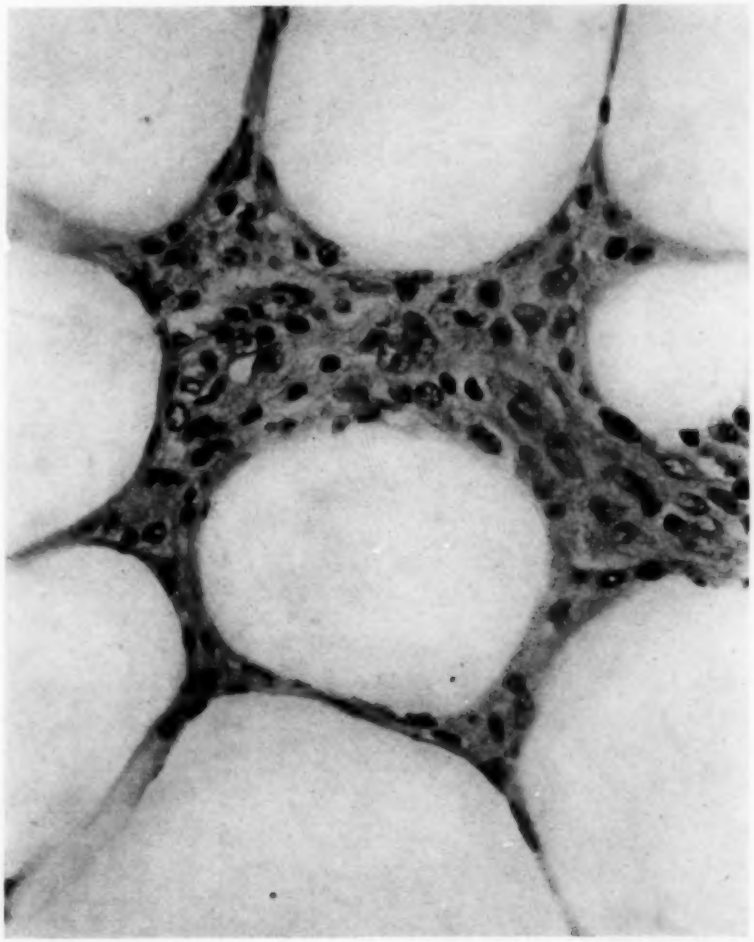

FIG. 2. High power photomicrograph (× 500) showing edema, thickening, and chronic inflammation of the fibrous tissue between the fat cells.

eosinophile. The sedimentation rate was 30 mm. at one hour. One blood culture showed no growth.

Blood Mazzini and Kahn reactions were negative. The spinal fluid Kahn reaction was doubtful, and a trace of globulin was found by the Pandy and Ross-Jones methods. The spinal fluid total protein was 34. The colloidal gold reaction was 1100000000.

A Gram stain from the throat lesion revealed a moderate number of pus cells and gram-positive cocci. No Vincent's organisms were found. Smears for tubercle bacilli and dark field examinations for *Treponema pallidum* were negative.

A tentative diagnosis of infectious granuloma was made, and a biopsy was taken from one of the leg lesions.

Pathological Report. Gross examination revealed an elliptical strip of skin measuring 3.5 by 1.4 by 1.0 cm., containing an irregular, wrinkled, slightly elevated, red area in the central portion measuring 1.3 by 1.0 cm. The surface showed no ulceration or scaling. The cut surface showed a few, tiny, red areas in the subcu-

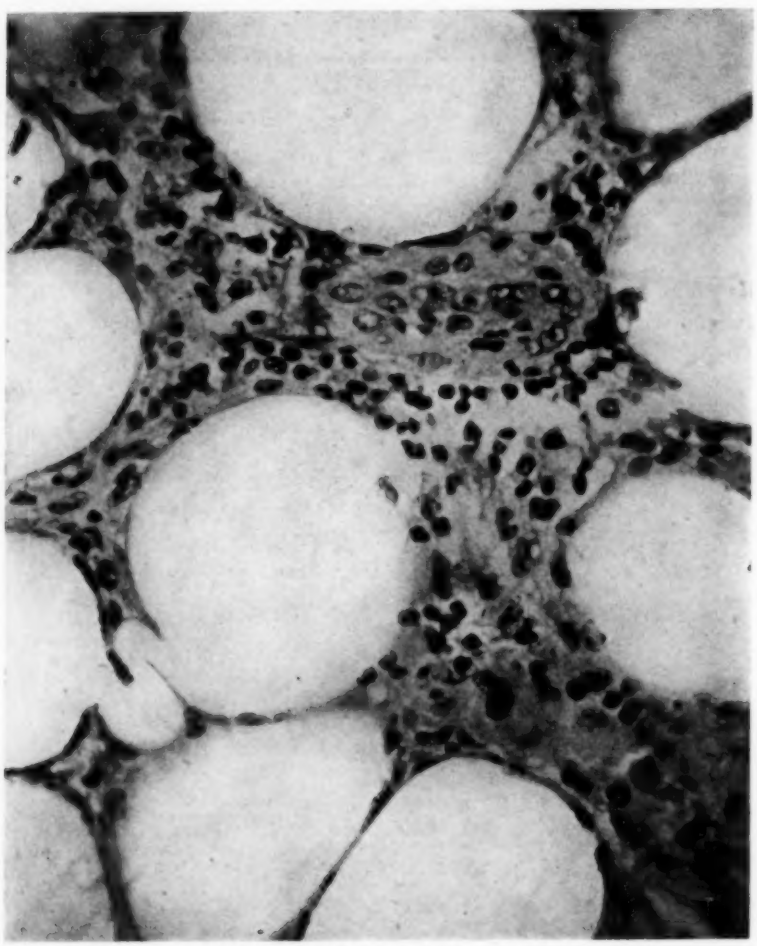

FIG. 3. High power photomicrograph (× 500) showing the granulomatous character of the lesion.

taneous fat. The fatty tissue was firm and nodular, but no well-defined tumor was seen.

Microscopic examination revealed an unusual picture resembling fat necrosis in general appearance. The subcutaneous nodule was made up almost entirely of fatty tissue arranged in poorly outlined lobules separated by fibrous strands. Many fat cells were necrotic, and numerous large monocytic cells filled with lipoid material were scattered through the tissue. The fibrous tissue between the fat cells was thick and edematous, and it contained a heavy sprinkling of lymphocytes and monocytes and a

few eosinophiles, plasma cells and segmented neutrophiles. Some of the tissue cells were large, swollen, and granular, resembling reticular cells. A few mitotic figures were seen in these cells. In a few small areas a granulomatous reaction made up of young fibrous tissue containing a few small collections of chronic inflammatory cells and one or two multinucleated giant cells was noted. There was marked increase in the fibrous tissue surrounding a few of the large blood vessels. A few of the large blood vessels and many of the smaller vessels showed infiltration of lymphocytes and monocytes through the walls and in the perivascular spaces. A few of the smaller vessels showed rather striking fibrinoid degeneration. The overlying epithelium was not remarkable. The corium contained a few collections of chronic inflammatory cells particularly around the small blood vessels. No other changes were noted in the skin.

As most of these pathologic changes have already been described, no attempt is made to show all of them in the accompanying photomicrographs. Low and high power photomicrographs of an area regarded as "representative" of the lesion and a high power photomicrograph of a granulomatous area are shown.

Course. The patient was given 40,000 units of penicillin every three hours for seven and one-half days, a total dosage of 2,400,000 units. Her course during several weeks of hospitalization was variable. The condition of the right eye and the throat lesions improved only temporarily. Her temperature ranged between 97.6° F. and 99.6° F. Repeated Mazzini and Kahn reactions were again negative. It was felt that the penicillin had not affected the course of the disease.

In view of the diagnosis, the patient was advised to refrain from all medication and particularly cautioned to avoid iodides and bromides. She was seen again in approximately six weeks after discharge from the hospital, at which time the ulcer in the throat had healed but two smaller ones had appeared in the gum and buccal mucous membrane. The swelling of the eye had almost entirely subsided, and the patient stated that she felt considerably better. The nodules in the leg had almost disappeared. The skin over the lesions was slightly darker than the surrounding skin and showed slight pitting.

Comment

The case is remarkable in several respects. The ulceration of the throat and the blepharitis of the right eye are findings which have not been reported in other cases.

This patient took a great many drugs, several of which contained iodine, and she also used iodized salt. After she discontinued this practice, she had a definite remission of symptoms. We feel that the excessive use of halogens as an etiological factor, as reported in the literature, may be substantiated by our observations in this case. Penicillin, the use of which, as far as we know, has not been previously reported in this condition, was of no value.

Summary

A case of relapsing febrile nodular nonsuppurative panniculitis in a 35 year old woman is reported. She had multiple ulcers in her throat and blepharitis of the right eye. There was a definite history of halogen ingestion, and the patient showed marked improvement after discontinuation of all medication. Penicillin therapy (2,400,000 units in seven and one-half days) did not affect the course of the disease.

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3. Rosenberg, W. A., and Cohen, T. M.: Relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian disease), Illinois Med. Jr., 1942, lxxxi, 59–62.
4. Arnold, H. L., Jr.: Nodular nonsuppurative panniculitis (Weber-Christian disease); preliminary report of case controlled by sulfapyridine, Arch. Dermat. and Syph., 1945, li, 94–99.
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6. Bailey, R. T.: Relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian disease), Jr. Am. Med. Assoc., 1937, cix, 1419–1425.
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EDITORIAL

RADIOACTIVE IODINE: PHYSIOLOGICAL AND CLINICAL STUDIES

SINCE 1946 radioactive isotopes of many varieties have become increasingly available to the investigator and clinician as a result of their release for distribution from the atomic energy pile at Oak Ridge, Tennessee. An upsurge of interest in the diagnostic and therapeutic applications of these agents has occurred. Two among the many available elements, radiophosphorus and radioiodine, have already found a distinct place in the modern therapeutic armamentarium. The behavior of these isotopes, among the earliest to be produced artificially, has been extensively studied in vitro as well as in vivo in animal and human subjects. The data thus obtained offered a basis for further clinical trial and investigation. The purpose of this brief summation is to review some of the pertinent physiological and clinical data which have been accumulated concerning radioactive iodine.

In 1934 Joliot and Curie [1] reported their discovery of artificial radioactivity and in the same year Fermi [2] was able to produce the first radioactive isotope of iodine. Twelve distinct isotopes of radioiodine have been described.[3] These, in common with all radioactive isotopes, behave, in a biological system, in a manner identical with the stable element. They are distinguished, one from the other, by their different atomic weights and by designation of their half-life period. All radioactive elements are unstable and hence as their nuclei emit radiations they undergo decay and transmutation. It can be shown mathematically that the time required for the complete decay and disappearance of a sample of radioactive material approaches infinity, regardless of the rate constant of this decay. In describing radioactive materials, therefore, it has been found convenient to refer to the half-life, the length of time which will elapse before half of the material initially present will have undergone transmutation. Of the twelve isotopes of iodine referred to, only two have been used extensively in biological and clinical investigation. One has an atomic weight of 130 (I^{130}) and a half-life of 12.5 hours; the other an atomic weight of 131 (I^{131}) and an eight-day half-life. Both are produced by the bombardment of metallic tellurium with deuterons. Radioiodine, like roentgen-rays, emits both beta and gamma rays. The latter are apparently less important for therapeutic purposes. The beta rays on the other hand, having a penetrating power of only a few millimeters will exert their maximum effect only over a small area when, as in the case of the thyroid, they are concentrated within the follicles. Extensive clinical application of a radioactive isotope is obviously distinctly related to its half-life period. Earlier studies with I^{130} were possible only

[1] JOLIOT, F., and CURIE, I.: Artificial production of a new kind of radio-element, Nature, 1934, cxxxiii, 201.

[2] FERMI, E.: Radioactivity induced by neutron bombardment, Nature, 1934, cxxxiii, 757.

[3] CHAIKOFF, I. L., and TAUROG, A.: Application of radioactive iodine to studies in iodine metabolism and thyroid function. *In* The Use of Isotopes in Biology and Medicine, 1948, University of Wisconsin Press, Madison.

in clinics located in close proximity to the cyclotron in which the element was produced. The eight-day isotope, I^{131}, now produced in adequate quantity by the atomic energy pile at Oak Ridge has extended the applicability of this element.

Physiological and clinical studies with radioiodine are fundamentally based upon the observations of Marine and his associates who, in 1915 and 1916,[4, 5] demonstrated the unique ability of the thyroid selectively to collect relatively large quantities of this element. The use of a labelled isotope has shed additional light upon certain basic problems associated with the metabolism of iodine. Such studies have usually been carried out with tracer doses of the isotope inadequate to produce a radiation effect upon the tissues, but nevertheless active enough to be detected by physical means. Localization as well as quantitation of radioiodine has been accomplished through the use of Geiger-Muller counters applied to the surface of the body over numerous areas. Additional information has been accumulated through the technic of autoradiography first employed by Hamilton, Soley and Eichorn.[6] By this ingenious method sections of thyroid containing radioiodine are found to produce a characteristic picture when placed against photographic film. Subsequent comparison of the developed film with identical histological sections permits localization of the isotope. Excretion of the element in urine and feces can be detected and quantitated by the Geiger counter.

It may be of interest to detail some of the pertinent information recently acquired by these methods. Werner, Quimby and Schmidt[7] observed, in a group of 30 normal individuals, that the average uptake of radioiodine by the thyroid was approximately 21 per cent of the ingested dose. In a group of 39 patients with thyrotoxicosis the average uptake was found to be approximately 58 per cent. Three individuals with non-toxic nodular goiters had an average uptake of 19 per cent, a figure closely approximating the normal. Five patients with hypothyroidism, on the other hand, had an average uptake of only 3 per cent. Other studies of similar character have yielded essentially similar results. It is apparent that the collection of iodine by the thyroid varies with the functional state of the gland. Such information has not only diagnostic value, but is of considerable therapeutic importance as will be emphasized below. It has been possible to duplicate these results by experimental means. Hertz et al.[8, 9] produced hyperplasia of the

[4] MARINE, D.: Quantitative studies on the in vivo absorption of iodine by dogs' thyroid glands, Jr. Biol. Chem., 1915, xxii, 547.

[5] MARINE, D., and ROGOFF, J. M.: The absorption of potassium iodide by the thyroid gland in vivo following its intravenous injection in constant amounts, Jr. Pharmacol. and Exper. Therap., 1916, viii, 439.

[6] HAMILTON, J. G., SOLEY, M. H., and EICHORN, K. B.: Deposition of radioactive iodine in human thyroid tissue, Univ. California Publ. Pharmacol. (No. 28), 1940, i, 339.

[7] WERNER, S. C., QUIMBY, E. H., and SCHMIDT, C.: The clinical use of radioactive iodine, Bull. N. Y. Acad. Med., 1948, xxiv, 549.

[8] HERTZ, S., ROBERTS, A., MEANS, J. H., and EVANS, R. D.: Radioactive iodine as an indicator in thyroid physiology. II. Iodine collection by normal and hyperplastic thyroids in rabbits, Am. Jr. Physiol., 1940, cxxviii, 565.

[9] HERTZ, S., and ROBERTS, A.: Radioactive iodine as an indicator in thyroid physiology. III. Iodine collection as a criterion of thyroid function in rabbits injected with thyrotropic hormone, Endocrinology, 1941, xxix, 82.

thyroid in animals by the feeding of a diet high in nitrile content (cabbage), and by the administration of the thyrotropic hormone of the pituitary. These hyperplastic glands were observed to have a greater affinity for iodine than the normal thyroid. Quantitation of the urinary excretion of the isotope offers adjunct evidence concerning iodine retention by the gland and is found to vary inversely with the percentage uptake by the thyroid.

Variations in the uptake of iodine by the thyroid can be produced by other experimental means some of which are of clinical interest. LeBlond et al.[10] noted that the exposure of rats to cold led to greater collection of iodine than normal and a doubling of the rate of excretion of iodized products. Antithyroid drugs, such as thiouracil and related compounds, first introduced in 1943,[11] are known to produce acinar hyperplasia paradoxically associated with a decrease in basal metabolic rate. The combined use of such compounds with radioiodine has resulted not only in verification but also extension of previous pharmacological hypotheses. Franklin, Lerner and Chaikoff [12] demonstrated that the feeding of thiouracil depresses the uptake of radioiodine by the rat thyroid and likewise retards its transformation into diiodotyrosine, and thyroxin. In this manner thiouracil blocks the formation of an iodinated hormone. Discontinuance of the drug was followed in a short time by a return to normal of the iodine concentrating capacity of the gland.

Clinicians have been puzzled for many years by the paradoxical yet beneficial effect of iodine upon patients whose thyroids were avid for the material and rapidly secreted the absorbed element as thyroid hormone. Rawson et al.[13] utilized radioiodine to study this phenomenon. In a typical patient with Graves' disease, administration of a tracer dose of radioiodine resulted in the urinary excretion of only 16.3 per cent indicative of a marked avidity for the drug. After treatment with thiouracil urinary excretion rose to 73.5 per cent. Treatment was continued with the combined use of thiouracil and radioiodine. Repeated urine studies indicated that virtually all of the labelled iodine was being excreted. At operation the gland was found to contain virtually no radioiodine. Yet, in spite of this, histological examination revealed involution of the hyperplastic gland. Rawson concluded that iodine exerts two actions on the thyroid, an iodinating action and an involuting one, in hyperthyroidism and that these two actions can be separated, one from the other, by means of thiouracil.

Many additional basic studies have been carried out with these agents which space limitations forbid mention of. Nevertheless, it is apparent

[10] LeBlond, C. P., Gross, J., Peacock, W., and Evans, R. D.: Metabolism of radioiodine in the thyroids of rats exposed to high and low temperatures, Am. Jr. Physiol., 1944, cxl, 671.

[11] Astwood, E. B.: Treatment of hyperthyroidism with thiourea and thiouracil, Jr. Am. Med. Assoc., 1943, cxxii, 78.

[12] Franklin, A. L., Lerner, S. R., and Chaikoff, I. L.: The effect of thiouracil on the formation of thyroxine and diiodotyrosine by the thyroid of the rat with radioactive iodine as an indicator, Endocrinology, 1944, xxxiv, 265.

[13] Rawson, R. W., Moore, F. D., Peacock, W., Means, J. H., Cope, O., and Riddell, C. B.: Effect of iodine on the thyroid gland in Graves' disease when given in conjunction with thiouracil: A two-action theory of iodine, Jr. Clin. Invest., 1945, xxiv, 869.

that such information constituted an important foundation for clinical application of the various isotopes of iodine. Hamilton and Lawrence,[14] in 1942, reported that a single dose of 300 microcuries of I^{131}, injected subcutaneously, produced almost complete destruction of a dog's thyroid without pathological evidence of damage to any other vital tissues. This dose represented approximately 30 times the single dose which would be given to man. It is this destructive effect on thyroid tissue which is the basis for the therapeutic application of radioiodine. The selective internal irradiation achieved by radioiodine is obviously distinctly more precise and localized than external irradiation by roentgen-rays which had been in use, to a certain extent, for a number of years.

The first clinical application of radioiodine was in the treatment of thyrotoxicosis. In 1942 Hertz and Roberts [15] and Hamilton and Lawrence [14] reported observations on the treatment of small groups of such patients. Since then studies on several additional groups of patients have been reported in the literature. Nevertheless, even today the total number of individuals studied is relatively small. Before discussing some of the reported observations it may be well to review certain of the problems associated with the clinical use of radioiodine. Reference has already been made to the matter of selection of the suitable isotope. The greater availability of I^{131} and its longer half-life have made this isotope the one of choice in most recent studies. The mode of administration has usually been per os, in aqueous solution.

Calculation of proper dosage has constituted a great problem and as a result earlier studies in which certain variables were not determined must be analyzed in this light. The variables to be taken into account in determining effective dosage include, in addition to the number of millicuries of isotope administered, the percentage uptake by the gland, its size and the rate of elimination from the thyroid. The effective dose can be expressed in terms of equivalent roentgens. This is determined, theoretically, by assuming an even distribution of so many microcuries per gram of thyroid gland. Preliminary calculations which are in the realm of the radio-physicist must be made prior to administration of the isotope. The clinician contemplating the use of radioiodine should be assured of the collaboration of a physicist.

Since radioiodine uptake by the thyroid is influenced by previous iodine or antithyroid drug therapy, it is essential, for maximum collection, that such drugs be withdrawn for at least a two-week period prior to the administration of the isotope. Preliminary tracer studies should be done to determine percentage uptake in the particular patient. Estimation of gland size is accomplished by palpation, keeping in mind, for reference, that the average normal thyroid has a weight of 25 to 30 grams. Werner, Quimby and Schmidt [7] utilize plasticine models of various sizes for this admittedly crude

[14] HAMILTON, J. G., and LAWRENCE, J. H.: Recent clinical developments in the therapeutic application of radio-phosphorus and radio-iodine, Jr. Clin. Invest., 1942, xxi, 624.

[15] HERTZ, S., and ROBERTS, A.: Application of radioactive iodine in therapy of Graves' disease, Jr. Clin. Invest., 1942, xxi, 624.

method of estimation. These investigators have proposed a formula for determining radiation dosage based upon all the variables mentioned above. In terms of I^{131} they suggest a total radiation dose of approximately 6,000 equivalent roentgens or approximately 100 or more microcuries per gram of gland tissue.

It will be of interest to review briefly some of the clinical data obtained in the treatment of thyrotoxicosis. In 1946 Hertz and Roberts [16] reviewed experiences with a group of 29 cases which had been observed since 1941. These patients were treated with a mixture of I^{130} and I^{131} consisting predominantly of the former. The total radioactivity administered varied between 0.7 and 28 millicuries. In 19 cases this was given in a single dose and in the remaining 10 in divided doses. All patients received stable iodine in the form of saturated solution of potassium iodide for varying periods after the administration of the radioisotope. The rationale for the latter procedure was the assumption that continued administration of stable iodine would reduce the rate of release of the isotope from the gland. Subsequent experience indicated that this procedure was probably unnecessary. Therapeutic benefits observed in this series were definitely attributable to the radioisotope. Twenty patients, followed for periods up to four years, were considered cured by all clinical and laboratory standards. In the remaining nine the treatment was considered ineffective. Five of these patients, who were subsequently sub-totally thyroidectomized, developed post-operative hypometabolism. No unusual complications were noted in the entire group. The incidence of successful therapy in this group, therefore, was 69 per cent.

Chapman and Evans [17] treated 22 patients with thyrotoxicosis during the period 1943 to 1945. These patients received 0.5 to 1 millicurie of I^{130} per estimated gram of thyroid tissue. The average total dose per patient was 40 to 50 millicuries. Fourteen patients responded well to a single dose; three required two doses and five had to be given three doses. No other therapy was used. Four patients subsequently developed myxedema and two, although improved, still were mildly hyperthyroid. Werner, Quimby and Schmidt [7] have treated 40 patients with toxic goiter with I^{131}. Eighteen had received no previous treatment, while 22 were recurrent after operation and had received antithyroid drug therapy for some time without satisfactory relief. All patients in this group received 3 to 4 millicuries of I^{131} which was calculated to give an effective dose of 3–5,000 equivalent roentgens. Maintenance of a standard dose resulted in patients with large thyroids receiving less radiation than others with smaller glands. This dosage schedule was deliberately adhered to for study purposes. Twenty-seven patients required only a single dose for complete control. Three additional patients responded well after a second dose. Six patients had been treated just prior to the

[16] Hertz, S., and Roberts, A.: Radioactive iodine as an indicator in the study of thyroid physiology. VII. The use of radioactive iodine therapy in hyperthyroidism, Jr. Am. Med. Assoc., 1946, cxxxi, 81.

[17] Chapman, E. M., and Evans, R. D.: The treatment of hyperthyroidism with radioactive iodine, Jr. Am. Med. Assoc., 1946, cxxxi, 86.

report and could not be evaluated. Four frank failures occurred. A successful result occurred therefore, in 30 of 34 patients, an incidence of 88 per cent. Analysis of the failures seems to implicate inadequate dosage attributable chiefly to disproportion between the size of the gland and the dose of isotope. Soley and Miller [18] have reported observations on 33 patients treated with I^{131} and followed for a period of three months to two years. Seventy-five per cent of the patients experienced a satisfactory remission.

In general, successfully treated patients experience a return to a normal basal metabolic rate by the end of the second or the middle of the third month after administration of the isotopes. In most instances the gland likewise returns to normal size in a similar period of time. Histological examination of such glands reveals loss of acinar tissue and resultant fibrosis. Soley and Miller performed serial ophthalmometric measurements on 26 of their patients. Seventeen exhibited no changes; one patient had a decrease in exophthalmos of 1.5 mm.; six patients had an increase in exophthalmos of 1.5 to 2.5 mm. Two patients developed severe exophthalmos and were later treated with thyroid extract. These authors believe that the changes in ocular findings compare favorably with those seen in other modes of therapy.

A consideration of the complications of radioiodine therapy must include not only the patient but also the physician and others associated with the treatment. The hazards to the patient may be of a more or less immediate nature or of long-term significance. There were no fatalities in any of the groups studied. Nor did tetany or loss of phonation occur. In a few instances symptoms resembling radiation sickness, of a transient character, occurred. Several instances of laryngeal irritation with cough and sore throat were observed and occasionally tenderness of the gland was present for a short time. In three patients of Werner, Quimby and Schmidt's group a transient increase in toxicity was seen. This was considered to be due to tissue necrosis with rapid release of large quantities of thyroid hormone. In several of the groups studied transient or sustained hypothyroidism developed. The relation of dosage to this phenomenon was usually evident. There were no disturbances of hematopoietic function in any of the reported cases. In view of the urinary excretion of the isotope studies of renal function were carried out in some instances, but no dysfunction was noted. Consideration of long term hazards with radioactive isotope therapy must include mention of the possibility of late malignancy. It is the consensus of opinion based, not only on isotope therapy, but also on previous experience with the roentgen treatment of thyrotoxicosis, that later malignant changes are unlikely.

Workers with radioactive isotopes must be fully cognizant of the hazards of excessive radiation. Rules for health protection issued by the Atomic

[18] SOLEY, M. H., and MILLER, E. R.: Treatment of Graves' disease with radioactive iodine, Med. Clin. N. Am., 1948, 3–17.

Energy Commission should be followed in any laboratory or clinic using these materials. During the first 24 to 72 hours after administration of radioactive iodine the patient's urine will be radioactive and measures for proper isolation and disposal must be taken.

The physician charged with the responsibility of the proper management of the patient with thyrotoxicosis has, today, a choice of three relatively satisfactory methods of therapy. Surgical management has steadily improved and in some clinics operative mortality has been reduced to under 1 per cent. Nevertheless, the ordeals attendant upon an operation remain. The introduction of propylthiouracil, with consequent diminution of toxic reactions, has improved the outlook for the medical management of the disease. Such therapy must often be maintained, however, over a period of a year or more with some uncertainty still existing concerning the permanence of remission following discontinuance of the drug. With radioiodine therapy problems of dosage still remain to be clarified. In addition, although the probability of late malignancy seems slight, a further period of time must elapse before this doubt can be resolved with certainty. Most workers in the field agree that, at present, isotope therapy should be used only in those centers equipped for adequate follow-up studies as well as facilities for careful measurement of dosage, and protection of personnel against radiation hazards. It is of course obvious that each of these methods of therapy is aimed at an etiology which is still imperfectly understood. The clarification of etiological mechanisms may in the future point the way toward an even more rational therapeutic attack upon the disease.

One can hardly leave the subject of radioactive iodine therapy without brief mention of its use in malignancy of the thyroid. Internal irradiation of neoplastic thyroid tissue in the neck as well as in distant metastatic foci would, at first glance, appear to offer considerable therapeutic possibilities. However, in 1940, Hamilton et al.[6] noted on clinical trial that the isotope was not deposited within carcinomatous areas of the gland. Subsequently, however, Keston et al.[19] were able to demonstrate an appreciable uptake of the isotope not only in well-differentiated metastases of an adenocarcinoma of the thyroid but also a small uptake by less well differentiated metastases in the same case. Seidlin, Marinelli and Osbry [20] have reported treatment of a patient with adenocarcinoma of the thyroid which was simultaneously accompanied by signs of hyperthyroidism. The thyrotoxicity was apparently due to hyperfunctioning metastases since the gland itself had been completely removed. Over a period of time this patient received 75 millicuries of I^{130} and 65 millicuries of I^{131}. Observation of the patient for three years revealed no clinical evidence of renal or other visceral involvement. The hyperthyroidism responded fully, but the metastases, although controlled, did not

[19] Keston, A. S., Ball, R. P., Frantz, V. K., and Palmer, W. W.: Storage of radioactive iodine in a metastasis from thyroid carcinoma, Science, 1942, xcv, 362.

[20] Seidlin, S. M., Marinelli, L. D., and Osbry, E.: Therapeutic effect of radioactive iodine on functioning metastases of thyroid adenocarcinoma, Jr. Am. Med. Assoc., 1946, cxxxii, 838.

disappear. This case is of further interest in that it demonstrated that massive dosages of radioactive iodine, far in excess of currently used dosages in hyperthyroidism, failed to produce any deleterious effects upon the kidney or hematopoietic tissue during a three year period of observation.

The largest group of cases of malignant disease of the thyroid treated with radioiodine reported to date is that of Marinelli et al.[21] These investigators studied the uptake of radioiodine in 19 cases of thyroid carcinoma. The extent of iodine collection appears to be related to the histopathology of the tumor. In general, well differentiated tumors absorb more of the isotope than anaplastic neoplasms. On the basis of the incidence of various histological types of thyroid malignancies only about 15 per cent of thyroid cancers may be expected to accumulate radioactive iodine to some degree. In view of the well known pleomorphism of thyroid cancer a decision concerning the therapeutic value of radioiodine cannot be based on a single small biopsy, but should be made only after preliminary tracer study. Future investigations into the therapeutic application of radioiodine in thyroid malignancy will be concerned with methods for increasing the iodine collecting properties of the tumor. At present surgical removal of as large a portion of malignant and normal thyroid tissue as possible is indicated, since this not only diminishes the amount of tissue to be irradiated, but may also increase the efficiency of subsequent uptake of the isotope. The preliminary use of thyrotropic hormone as well as means for temporarily blocking the renal excretion of the isotope is at present under investigation.

M. S. S.

[21] Marinelli, L. D., Foote, F. W., Hill, R. F., and Hocker, A. F.: Retention of radioactive iodine in thyroid carcinomas: Histopathologic and radio-autographic studies, Am. Jr. Roentgenol., 1947, lviii, 17.

REVIEWS

Principles of Hematology. 3rd Ed. By RUSSELL L. HADEN. 366 pages; 15.5 × 24 cm. Lea & Febiger, Philadelphia. 1946. Price, $5.00.

The third edition of this volume presents a brief and somewhat elementary survey of the field of Hematology. The merit of a simple introduction to a complex field such as this cannot be denied but the presentation would be distinctly more valuable with the addition of a carefully selected bibliography designed to assist the interested reader. The bibliography is quite scanty and most references are to reports published prior to 1939. Many recent developments in hematology such as the use of folic acid in the macrocytic anemias and nitrogen mustard in the leukemias and lymphomata are not discussed at all. The book is abundantly illustrated but most of the illustrations, although technically good, are in black and white and are insufficiently magnified to be of any great help to the novice for whom the book is intended.

M. S. S.

The Management of Obesity. By LOUIS PELNER, M.D., Associate Physician. Green-Point Hospital, Brooklyn, New York. 144 pages; 15 × 22.5 cm. Personal Diet Service, New York, N. Y. 1946.

This is a small, handy, readable book that tells in a few pages many of the elementary facts about the problems of overweight due to excess fat. Actuarial philosophy is liberally added in the early pages. The short chapters bounce somewhat unevenly from practicalities of treatment to etiological association with some rare diseases. Unnecessary emphasis is given to 'endogenous' obesity and to elaborate recommendations regarding exercise. There are some effective diagrams and a useful summary of nutritional factors and values.

C. B. A.

Viral and Rickettsial Infections of Man. Edited by THOMAS M. RIVERS, M.D., Director of the Hospital, The Rockefeller Institute for Medical Research. 587 pages; 26.5 × 18 cm. J. B. Lippincott Company, Philadelphia. 1948. Price, $5.00.

The editor has assembled an imposing list of authorities to write the different sections of this volume. Nearly all of the better known names of American workers in the viral and rickettsial diseases are listed among the contributors. The book is an authoritative statement of the status of our knowledge in this field. So rapid have been the advances in recent years that such a symposium will greatly lighten the task of the physician who otherwise would have to search the profuse and widely scattered journal literature.

The first seven chapters are devoted to the methods employed in the study of viral and rickettsial agents. After an introductory chapter by Thomas M. Rivers on the general nature of these agents and the infections due to them there are chapters on physical and chemical procedures (W. M. Stanley and Max A. Lauffer); serological reactions (Joseph E. Smadel); chick-embryo technics (E. W. Goodpasture and G. John Buddingh); propagation in tissue culture (John F. Enders); epidemiology (Kenneth F. Maxcy); and bacteriophages (A. D. Hershey and J. Bronfenbrenner). These chapters constitute a most valuable summary and critique of the investigative methods in this difficult field. Every student of the viral and rickettsial disease problems will benefit by this well organized presentation.

The remainder of the book, approximately 400 pages, is devoted to the different diseases and disease groups of known viral and rickettsial origin. These chapters are not written by clinicians for clinicians but by scientific investigators who are interested primarily in disease. A uniform outline has been employed: Introduction;

history; clinical picture; pathological picture; experimental infection, host range; etiology; diagnosis; treatment. The emphasis is on the characteristics of the etiological agent, the immunologic processes concerned, the diagnostic procedures in man and animals and on epidemiology. It is of course these aspects of these diseases in which research has been and is so active and so fruitful.

The selection of authors has naturally been on the basis of their contributions to knowledge of these aspects of the diseases described. Other investigators, pathologists, bacteriologists, internists will find the chapters on the separate diseases an invaluable reference.

The sections on the "clinical picture" are of varying value. On the whole they make little attempt to more than outline the common clinical characteristics. References to the clinical literature are relatively few. Questions of treatment are often sketchily dealt with, and in some instances appear too dogmatic. The principles of disease control are discussed but not the practical details of application. In brief, the practicing physician and the field worker in disease prevention will gain deeper understanding of basic processes in the diseases discussed but not all that he might want in clinical detail, for use at the bedside, or of practical methods for a control program.

Within its scope there is no single text which is so adequate. It fills a very real need and should meet a warm welcome.

M. C. P.

BOOKS RECEIVED

Books received for September are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

A–B–C's of Sulfonamide and Antibiotic Therapy. By PERRIN H. LONG, M.D., F.R.C.P., Professor of Preventive Medicine, The Johns Hopkins University School of Medicine, etc. 231 pages; 19 × 11.5 cm. 1948. W. B. Saunders Company, Philadelphia. Price, $3.50.

Bronchiogenic Carcinoma and Adenoma, with a Chapter on Mediastinal Tumors. By B. M. FRIED, M.D., Associate Attending Physician, Montefiore Hospital for Chronic Diseases, New York. 306 pages; 23.5 × 16 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $6.00.

Changing Disciplines: Lectures on the History, Method and Motives of Social Pathology. By JOHN A. RYLE, M.D., Professor of Social Medicine in the University of Oxford, etc. 123 pages; 19 × 12.5 cm. 1948. Oxford University Press, New York. Price, $3.75.

Clinical Roentgenology of the Digestive Tract. 3d Ed. By MAURICE FELDMAN, M.D., Assistant Professor of Gastroenterology, University of Maryland, etc. 901 pages; 24 × 16 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $8.00.

Detailed Atlas of the Head and Neck. By RAYMOND C. TRUEX, M.S., Ph.D., Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University; and CARL E. KELLNER, Artist, Department of Anatomy, College of Physicians and Surgeons, Columbia University. 162 pages; 31.5 × 24.5 cm. 1948. Oxford University Press, New York. Price, $15.00.

Handbook of Orthopaedic Surgery. 3d Ed. By ALFRED RIVES SHANDS, JR., B.A., M.D., Medical Director of the Alfred I. duPont Institute of the Nemours Foundation, Wilmington, etc.; in collaboration with RICHARD BEVERLY RANEY, B.A., M.D., Associate in Orthopaedic Surgery, Duke University School of Medicine, Durham, etc.; Illustrated by JACK BONACKER WILSON. 574 pages; 22.5 × 14.5 cm. 1948. The C. V. Mosby Company, Saint Louis. Price, $6.00.

Hospital Trends and Developments, 1940–1946. Edited by ARTHUR C. BACHMEYER, M.D., Director, University of Chicago Clinics, etc., and GERHARD HARTMAN, Ph.D., Superintendent, University Hospitals, etc. 819 pages; 24.5 × 16 cm. 1948. The Commonwealth Fund, New York. Price, $5.50.

Lecciones de Patología Médica (Enfermedades del Higado). Tomo VI. By DR. C. JIMENEZ DIAZ. 998 pages; 25 × 17.5 cm. 1948. Editorial Cientifico-Medica, Madrid.

Management in Obstetrics. By ANDREW M. CLAYE, M.D., F.R.C.S., F.R.C.O.G., Professor of Obstetrics and Gynaecology, University of Leeds, etc. 186 pages; 19 × 12.5 cm. 1948. Oxford University Press, New York. Price, $3.75.

Medical Research in France During the War (1939–1945). Thirty articles gathered and presented by JEAN HAMBURGER, Professor agrégé à la Faculté de Médecine, Médecin des Hôpitaux de Paris. Foreword by PROFESSEUR PASTEUR VALLERY-RADOT, Membre de l'Institut. 306 pages; 25.5 × 16.5 cm. (paper-bound). 1948. Éditions Médicales Flammarion.

Microbiology and Pathology. 4th Ed. By CHARLES F. CARTER, B.S., M.D., Instructor in Pathology and Applied Microbiology, Parkland Hospital School of Nursing, Dallas, etc. 845 pages; 22.5 × 14.5 cm. 1948. The C. V. Mosby Company, Saint Louis. Price, $5.00.

Occupational Marks and Other Physical Signs: A Guide to Personal Identification. By FRANCESCO RONCHESE, M.D., Instructor in Dermatology, Boston University School of Medicine, etc.; Foreword by JOHN G. DOWNING, M.D., Professor of Dermatology, Boston University School of Medicine, etc. 181 pages; 23.5 × 16 cm. 1948. Grune & Stratton, Inc., New York. Price, $5.50.

Pharmacology. 3d Ed. By J. H. GADDUM, ScD., F.R.S., M.R.C.S., L.R.C.P., Professor of Pharmacology in the University of Edinburgh. 504 pages; 22.5 × 14 cm. 1948. Oxford University Press, New York. Price, $8.00.

Polio and Its Problems. By ROLAND H. BERG, with a Foreword by BASIL O'CONNOR, President, The National Foundation for Infantile Paralysis, Inc. 174 pages; 23.5 × 16 cm. 1948. J. B. Lippincott Company, Philadelphia. Price, $3.00.

A Practical Manual of the Diseases of the Chest. 3d Ed. By MAURICE DAVIDSON, M.A., M.D. Oxon., F.R.C.P. Lond., Physician to the Brompton Hospital for Consumption and Diseases of the Chest, etc. 670 pages; 25 × 17.5 cm. 1948. Oxford University Press, New York. Price, $16.50.

Reticulosis and Reticulosarcomatosis: A Clinical and Pathological Study. By DR. P. VAN DER MEER and DR. J. ZELDENRUST, from the Medical Clinic of the University Hospital, Leyden, Holland, etc. 99 pages; 24.5 × 16 cm. 1948. Universitaire pers Leiden, Leyden, The Netherlands. Price: guilders 4.90.

Sterility and Impaired Fertility: Pathogenesis, Investigation and Treatment. 2nd Ed. By CEDRIC LANE-ROBERTS, C.V.O., M.S., F.R.C.S., F.R.C.O.G., Gynaecological Surgeon, Royal Northern Hospital, etc.; ALBERT SHARMAN, M.D., Ph.D., M.R.C.O.G., Senior Assistant Surgeon, Royal Samaritan Hospital for Women, Glasgow, etc.; KENNETH WALKER, M.A., M.B., B.C. (Cantab), F.R.C.S., F.I.C.S., Jacksonian Prizeman and Hunterian Professor, Royal College of Surgeons, etc.; B. P. WIESNER, D.Sc., Ph.D., F.R.S.E., Consulting Biologist, Royal Northern Hospital, and MARY BARTON, M.B., B.S., First Assistant to the Fertility Clinic, Royal Free Hospital, London. 400 pages; 22.5 × 14.5 cm. 1948. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $6.50.

Symposia on Nutrition of The Robert Gould Research Foundation. Volume 1: Nutritional Anemia. Edited by ARTHUR LEJWA. 194 pages; 23.5 × 15 cm. 1948. The Robert Gould Research Foundation, Inc., Cincinnati. Distributed without cost to individuals and organizations interested in nutritional problems.

COLLEGE NEWS NOTES

Proposal of Candidates

The By-Laws of the American College of Physicians require that proposals of candidates for election to Associateship or Fellowship be filed at least 60 days in advance of action by the Credentials Committee. The next meetings of the Committee are scheduled for February 26 and 27, 1949, and March 26, 1949.

Associates Should Attend A.C.P. Annual Session

Attendance at one or more Annual Sessions by Associates before proposal for advancement to Fellowship is prescribed by regulations of the Board of Regents of the American College of Physicians. This regulation was temporarily discontinued during World War II, from 1942 to 1946, because it became obviously impossible for Associates in the armed services to attend and because the Annual Sessions of the College had to be abandoned during part of that time. The regulation is now again in full effect. It is maintained that an Associate must display an abiding interest in the College and in internal medicine or its allied branches. There is no better way in which such an interest can be displayed than by attendance at the Annual Sessions of the College, accepted as the most important postgraduate week in the field on this Continent.

1948 Membership Roster Distributed

The Board of Regents and Officers of the American College of Physicians had hoped to be able to resume publication this year of a complete College Directory. This was found to be impossible, however, because of continued shortage of printing labor and excessively high production costs, and so authorization was given to print the 1948 Membership Roster, in which biographical data of members are omitted.

The Membership Roster contains lists of the Boards of Regents and Governors, Officers, and Committees; the full Constitution and By-Laws, as amended May 1, 1947, and April 22, 1948; a statement of the College's Awards and Fellowships; and the alphabetic and geographic (with specialty designations) rosters of members as of August 1, 1948.

The Roster has now been mailed to all members of the College in good standing. If any have failed to receive their copies, they are requested so to inform the Executive Secretary of the College. Also, it is desired that the Executive Secretary be notified of any corrections or omissions in the Roster listings.

A.C.P. Postgraduate Courses

Autumn, 1948 Schedule

It is gratifying to report that the postgraduate courses of the American College of Physicians on the Autumn, 1948 schedule have all been well supported and that there was even a further improvement in the quality, scope and teaching over the same preceding courses. There remain on the program two courses, No. 7, Cardiovascular Disease, Emory University School of Medicine, Atlanta, Bruce Logue, M.D., F.A.C.P., Director, one week—December 6–11; and No. 8, Gastro-enterology, Graduate Hospital of the University of Pennsylvania, Philadelphia, H. L. Bockus, M.D., F.A.C.P., Director, one week—December 6–11. At the time of preparation of this news item (October 13, 1948) both courses are still open for additional registrations.

Spring, 1949 Schedule

Following is the tentative schedule of courses under consideration by the Advisory Committee on Postgraduate Courses for the Spring of 1949.

(1) GASTRO-ENTEROLOGY—University of California Medical School and Stanford University School of Medicine, San Francisco, Calif.; T. L. Althausen, M.D., F.A.C.P., and Dwight L. Wilbur, M.D., F.A.C.P., Directors; one week, February 7–12.

This course is open for registration, although the outline is not published. These very capable Directors are organizing an outstanding course which should be exceedingly popular with members of the College, especially those from the West and Far West. Dr. Cecil Watson, Professor of Medicine at the University of Minnesota Medical School, will be one of the guest clinicians.

(2) HEMATOLOGY—Ohio State University College of Medicine, Columbus, Ohio; Charles A. Doan, M.D., F.A.C.P., Director; one week, February 14–19.

This is a repetition of previous, excellent courses that Dr. Doan has organized for the College. It is a course of exceptional merit in its field.

(3) PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE—University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Julius H. Comroe, Jr., M.D., F.A.C.P., Director; one week, May 9–14.

This is a repetition of the most unusual and popular course organized by Dr. Comroe one year ago when the registration rose to 189. It is planned for internists who are interested in learning why symptoms occur, how drugs act, and why and how clinical physiological tests are used in diagnosis. It is designed—not along lines of the theoretical physiology taught in many undergraduate medical schools—but rather along newer concepts of teaching dynamic clinical physiology to practicing physicians. The faculty will consist of many authorities from Philadelphia institutions, and also outstanding teachers and authorities from Boston, New York, Baltimore, Chicago, Cleveland, and elsewhere.

(4) INTERNAL MEDICINE—Massachusetts General Hospital, Boston, Mass.; James H. Means, M.D., F.A.C.P., Director; two weeks—dates yet to be determined.

Dr. Means is Jackson Professor of Clinical Medicine, Harvard Medical School, and Chief of Medical Services, Massachusetts General Hospital. He and his faculty are known everywhere for the excellence of their exceedingly fine work. They have not given a course for the College for a few years, and this will be an exceptional opportunity for members to take this fine course in Boston.

(5) CARDIOLOGY—Philadelphia Institutions; William G. Leaman, Jr., M.D., F.A.C.P., Director; one week—dates yet to be determined.

This course is under discussion with Dr. Leaman and other participating teachers in the Philadelphia area. The faculty will consist of leading teachers in Cardiology from various medical schools of Philadelphia and other institutions of the East. The course has been given on previous occasions with signal success.

(6) DISEASES OF THE CHEST—Creighton University School of Medicine and the University of Nebraska College of Medicine, Omaha, Nebr.; J. D. McCarthy, M.D., F.A.C.P., Director; one week—dates yet to be determined.

This course is still in the formative state, under discussion by the Director and members of the faculties of the two named institutions. It is possible that the title of the course may be changed. Watch these columns for further announcements.

(7) ELECTROCARDIOGRAPHY—Massachusetts General Hospital, Boston, Mass.; Conger Williams, M.D., Director; one week—dates yet to be determined.

This will be a repetition of the course given for the College by Dr. Williams during May, 1948. It is designed to acquaint the student with modern theory of electrocardiography and its clinical application. The opening days will be devoted to lectures on the theory of electrocardiography and an attempt will be made to present the current points of view. Since it is impossible to teach electrocardiographic interpretation in so short a time, the course should be limited to those who have had some previous experience in the field. By presenting many electrocardiograms from the laboratory, there will be sufficient material to cover the most important representative patterns. The chief aim of this course will be to teach interpretation based on current knowledge of the physiology of heart muscle. All the exercises in practical interpretation will include the new leads.

(8) ENDOCRINOLOGY—Tufts College Medical School, Boston, Mass.; Edwin B. Astwood, M.D., Director; one week—dates yet to be determined.

This course is still tentative on the schedule, but arrangements are being consummated through Dr. Robert P. McCombs, F.A.C.P., Director of Postgraduate Teaching at Tufts College Medical School. Dr. Astwood is Research Professor of Medicine at Tufts College Medical School, and Endocrinologist to the Pratt Diagnostic Hospital. He is a recognized authority in the field of Endocrinology and a teacher of note.

(10) MEDICAL ASPECTS OF RADIOACTIVITY—Bureau of Medicine and Surgery, U. S. Navy, Medical Department of the U. S. Army, the Armed Forces Special Weapons Project, the Atomic Energy Commission, the Air Force and the U. S. Public Health Service, Washington, D. C.; Lt. Col. Karl Houghton, (MC), USA, Chairman.

It is not yet determined whether the course will be one, two, or three weeks in duration, nor have the dates been selected. The Surgeons General of the three services will coöperate wholeheartedly with the Armed Forces Special Weapons Project, and every effort is being made to procure the best talent available. Only a nominal registration fee will be charged. No fee whatsoever will be charged to medical officers, regular and reserve, of the Army, Navy, and Public Health Service. Details of the course are not yet fully available. An effort will be made to include the nature of ionizing radiation as it relates to atomic fission, the methods of detection and evaluation of the hazard, the biological effects of radiation, the possibilities of protection and avoidance, and present concepts of treatment. It is an obligation of the medical profession to inform themselves in this very important subject.

A.C.P. REGIONAL MEETINGS

The *North Carolina* regional meeting of the College will take place at Chapel Hill on Friday, December 3, under the Governorship of Dr. Paul Whitaker, F.A.C.P. Edward McG. Hedgpeth, M.D., F.A.C.P., is chairman of the Program Committee.

The *Eastern Pennsylvania* regional meeting will take place in Philadelphia on December 10. Dr. Edward L. Bortz, F.A.C.P., the local Governor, has arranged an interesting program at the College of Physicians and Surgeons of Philadelphia, including a number of papers being presented that day in the A.C.P. postgraduate course in Gastroenterology (Henry L. Bockus, M.D., F.A.C.P., Director). A reception and dinner will be held in the evening at the Hotel Warwick.

The annual *Oklahoma* regional meeting was held at Tulsa on September 25, under the Governorship of Dr. Wann Langston, F.A.C.P., of Oklahoma City. Dr. LeRoy H. Sloan, F.A.C.P., Chicago, a Regent of the College, was the chief guest speaker and official representative of the Board. There were in attendance 38 Fellows from Oklahoma, 9 Fellows from other states, 11 Oklahoma Associates and one Associate from another state. In addition there were 59 guests, several of whom have proposals for membership now outstanding. Present also were the Deans of the Medical Schools of the University of Oklahoma and the University of Arkansas. A great deal of interest was displayed in the scientific program, in which papers were presented by Dr. William K. Ishmael, F.A.C.P., W. Floyd Keller, M.D., F.A.C.P., John H. Lamb, Jr., M.D., F.A.C.P., and Wann Langston, M.D., F.A.C.P.; Moorman P. Prosser (Associate); Arthur A. Hellbaum, M.D., Ph.D., and Cleve Beller, M.D., guests; Oklahoma City; D. W. Gillick, M.D., F.A.C.P., Talihina; E. Rankin Denny, M.D., F.A.C.P., and Samuel Goodman, F.A.C.P.; Paul Strong, M.D., and Averill Stowell, M.D., guests; Tulsa; Euclid M. Smith, M.D., F.A.C.P., Hot Springs, Ark.; LeRoy H. Sloan, M.D., F.A.C.P., Chicago; and Harold H. Jones, Sr., F.A.C.P., Winfield, Kans.

The *Iowa* regional meeting, at the Des Moines Club on October 9, was held under the Governorship of B. F. Wolverton, M.D., F.A.C.P., Cedar Rapids, who was ably assisted in the program arrangements by Drs. George E. Mountain, F.A.C.P., John C. Parsons, F.A.C.P., and Maurice J. Rotkow, F.A.C.P. Following a business meeting and luncheon, papers were presented by the following: Forest H. Coulson, M.D. (Associate), Burlington, Coronary Occlusion or Pulmonary Embolism?; Paul W. Berney, M.D. (Associate), Cedar Rapids, Senile Osteoporosis; Lawrence J. Halpin, M.D. (Associate), Cedar Rapids, Dosage Tolerance in Respiratory Allergy; Charles F. Lowry, M.D. (Associate), Council Bluffs, Fibrositis: Diagnosis and Treatment; Leon J. Galinsky, M.D., F.A.C.P., Des Moines, Bronchiogenic Carcinoma: A Clinical Dilemma; Arthur G. Lueck, M.D. (Associate), Des Moines, Etiology of Diabetes Mellitus: Current Concepts; P. G. Keil, guest, Des Moines, Angiocardiography; William B. Bean, M.D. (Associate), Iowa City, Cerebral Manifestations of Acute Myocardial Infarction; Henry Hamilton, M.D., guest, Iowa City, Cooley's Anemia; Leslie W. Swanson, M.D. (Associate), Mason City, X-Ray for Bronchial Asthma. A reception and dinner completed the program.

The first A.C.P. regional meeting in *Arkansas* was scheduled for October 30 at Hot Springs. Arless A. Blair, M.D., F.A.C.P., Fort Smith, Governor for Arkansas, presided at the banquet at which the speakers were Joseph T. Roberts, M.D., F.A.C.P., Dean of the University of Arkansas School of Medicine, and Dr. William D. Stroud, F.A.C.P., Philadelphia, A.C.P. Treasurer. Dr. Euclid M. Smith, F.A.C.P., was local Chairman of Arrangements. Dr. George B. Fletcher, F.A.C.P., presided over the afternoon meeting. The following papers were listed: A Report of 15 Cases of Tularemia with Special Reference to Results of Treatment, Captain Richard R. Taylor, (M.C.), U.S.A., guest, Hot Springs; Hemochromatosis—Case Report of a White Female without Diabetes Mellitus, Charles T. Chamberlain, M.D., F.A.C.P., Fort Smith; Adrenal Cortical Syndrome in Children, William A. Reilly, M.D., guest, Little Rock; Antibiotic Treatment of Pertussis, P. J. Almaden, M.D., Ph.D., guest, Little Rock; Current Problems in Research upon Nutritional Anemias, Paul L. Day, Ph.D., guest, Little Rock; The Myocarditis Problem, Robert H. Bayley, M.D., F.A.C.P., Oklahoma City, Okla.

The *Southeastern* Regional Meeting of the College, arranged through the cooperation of E. Dice Lineberry, M.D., F.A.C.P., Birmingham, Governor for Alabama, William C. Blake, M.D., F.A.C.P., Tampa, Governor for Florida, Carter Smith, M.D., F.A.C.P., Atlanta, Governor for Georgia, Robert Wilson, Jr., M.D., F.A.C.P., Charleston, Governor for South Carolina, and Jose J. Centurion, M.D., F.A.C.P., Havana, Governor for Cuba, will be held at the Academy of Medicine in Atlanta on December 4. William R. Minnich, M.D., F.A.C.P., Atlanta, is Chairman of the Committee on Arrangements. Dr. Walter W. Palmer, A.C.P. President, New York City, Dr. James E. Paullin, M.A.C.P., Atlanta, and Mr. Edward R. Loveland, A.C.P. Executive Secretary, are listed as speakers at the banquet in the Biltmore Hotel. The scientific session will include the following speakers: Paul E. Beeson, M.D., guest, Atlanta, Current Trends in Antibiotic Therapy; Walter Bauer, M.D., F.A.C.P., Boston, Diagnosis and Treatment of Gout; Walter H. Cargill, M.D., guest, Atlanta, Present-day Concepts of the Medical Treatment of Hypertension; David James, M.D., guest, Atlanta, The Management of Dicumarol Administration; Heinz Weems, M.D., and James Warren, M.D., guests, Atlanta, The Intracardiac Dynamics, as Illustrated by Diodrast Media (Moving Picture); Osler Abbott, M.D., guest, Atlanta, Management of Pulmonary Emphysema; Arthur Merrill, M.D., guest, Atlanta, Rôle of Potassium in Certain Medical and Surgical Conditions; William A. Smith, guest, Atlanta, Newer Drugs in the Treatment of Epilepsy.

Continuing the multi-state regional meetings so successfully started during the war, Governors and members of the College in Illinois, Indiana, Michigan, Minnesota and Wisconsin collaborated to produce the 1948 *Midwest* Regional Meeting at the Book-Cadillac Hotel, Detroit, on November 20. The host Governor was Dr. Douglas Donald, F.A.C.P., of Detroit, assisted by the Program Committee of which Dr. H. M. Pollard, F.A.C.P., Ann Arbor, was Chairman, and the Committee on Arrangements, Dr. Edward D. Spalding, F.A.C.P., Detroit, Chairman. The following presented papers: Gordon B. Myers, M.D., F.A.C.P., H. A. Klein, M.D., and T. Hiratzka, M.D., guests, Detroit, Correlation of Electrocardiographic and Pathologic Findings in Anterolateral Infarction; Franklin Johnston, M.D., guest, Ann Arbor, Common Errors in Interpretation of the Electrocardiogram; B. F. Ziegler, M.D., guest, Detroit, Diagnostic Problems in Congenital Heart Disease; Mitchell A. Spellberg, M.D., F.A.C.P., Chicago, Clinical Aspects of Unusual Cases of Small Bowel Disease; M. H. Streicher, M.D., guest, Chicago, Recent Trends in the Management of Chronic Ulcerative Colitis; Samuel F. Haines, M.D., F.A.C.P., and F. R. Keating, M.D., guest, Rochester, Minn., Use of Radio-iodine in the Treatment of Exophthalmic Goiter; Frank H. Bethell, M.D., F.A.C.P., Ann Arbor, Newer Methods in the Treatment of Leukemia; Frank Hartman, M.D., guest, Detroit, Problems in Internal Medicine—Studies with the Oxyhemograph (Continuous Recordings of Blood Oxygen); R. Frisch, M.D., guest, and Maurice A. F. Hardgrove, M.D., F.A.C.P., Madison, Wis., Evaluation of Newer Methods in the Diagnosis and Treatment of Peripheral Arterial Disorders; Richard B. Capps, M.D., F.A.C.P., Chicago, Clinical Aspects of Sequelae of Acute Hepatitis; Robert M. Kark, M.D., guest, Chicago, Present Status of Albumin Therapy in Chronic Hepatitis; D. Myers, M.D., guest, Detroit, Boeck's Sarcoid; Bradley M. Patten, M.D., guest, Ann Arbor, Micro-moving Pictures Showing Age Changes in the Character of the Embryonic Heart Beat; Thomas Francis, Jr., M.D., guest, Ann Arbor, Immunity to Poliomyelitis; Elwood A. Sharp, M.D., F.A.C.P., and E. H. Payne, M.D., guest, Detroit, The Effectiveness of Chloromycetin in the Treatment of Rickettsial Disease; Jerome W. Conn, M.D., F.A.C.P., Ann Arbor, Sweat Electrolytes in the Diagnosis of Abnormal Adrenal Cortical Function; W. P. Daines, M.D., guest, and Walter H. Nadler, M.D., F.A.C.P., Chicago, Routine Use of Insulin in Early Diabetes Mellitus; Walter L. Palmer, M.D., F.A.C.P., and W. Ricketts, M.D., guest, Chicago, Studies on the Effect of Roentgen Irradiation in Peptic Ulcer; R. H. Ebert, M.D., guest, J. J. Ahern, M.D., guest, and Robert G. Block,

M.D., F.A.C.P., Chicago, Development of Tuberculous Infection: In Vivo Observations in the Rabbit Ear Chamber; John B. Youmans, M.D., F.A.C.P., Chicago, The Nutritional Anemias in Practice; William D. Robinson, M.D., F.A.C.P., Ann Arbor, Nutritional Aspects of Rheumatoid Arthritis; J. R. McDonald, M.D., guest, Clinical Appraisal of Examination of the Sputum in Carcinoma of the Lung Aspects; J. L. Sims, M.D. (Associate), Madison, Wis., Pulmonary Adenomatosis, Its Clinical Diagnosis; R. M. Angle, M.D., guest, and Howard L. Alt, M.D., F.A.C.P., Chicago, Hepatitis without Jaundice in Infectious Mononucleosis; L. T. Iseri, M.D., A. J. Boyle, M.D., S. D. Jacobson, M.D., T. M. Batchelor, M.D., guests, and Gordon B. Myers, M.D., F.A.C.P., Detroit, Diagnosis of Uremia Due to Lower Nephron Nephrosis. Presiding officers included Dr. Frank J. Heck, F.A.C.P., Rochester, Minn., Dr. Karver L. Puestow, F.A.C.P., Madison, Governor for Wisconsin, Dr. Cecil M. Jack, F.A.C.P., Decatur, Governor for Southern Illinois, and Dr. Robert M. Moore, F.A.C.P., Indianapolis, Governor for Indiana. Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Regent, was Toastmaster in the evening. The distinguished guests included Edgar A. Guest, Detroit poet, Dr. Reginald Fitz, A.C.P. President-Elect, Dr. William S. Middleton, 1st Vice President, Dr. Ernest E. Irons, Regent, Dr. Walter L. Palmer, Chairman of the Board of Governors, and Mr. E. R. Loveland, Executive Secretary.

Specialty Board Notices

American Board of Internal Medicine, William A. Werrell, M.D., Asst. Secretary-Treasurer, 1 W. Main St., Madison 3, Wis. Oral examination at San Francisco on February 8, 9, and 10, 1949—closing date for acceptance of applications December 1, 1948. Oral at New York City on March 23, 24, and 25, 1949—closing date for acceptance of applications January 2, 1949. Oral at Philadelphia on June 1, 2, and 3, 1949—closing date for acceptance of applications January 2, 1949. Written examination on October 17, 1949—closing date for acceptance of applications May 1, 1949.

The American Board of Pediatrics, Inc., John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Rd., Rosemont, Pa. The next written examination will be held on January 7, 1949. Oral examinations are scheduled to be given at St. Louis, Mo., on February 18, 19 and 20, 1949, and at Baltimore, Md., on April 22, 23 and 24, 1949.

The American Board of Physical Medicine, Robert L. Bennett, M.D., Secretary-Treasurer, 30 N. Michigan Ave., Chicago 2, Ill. The examination period will be two days immediately prior to the annual convention of the American Medical Association, June, 1949, at Atlantic City, N. J. Applications must be complete and in the hands of the Secretary-Treasurer three months prior to this date.

American Board of Psychiatry and Neurology, Inc., F. J. Braceland, M.D., Secretary-Treasurer, 102 2nd Ave., S.W., Rochester, Minn. The next semi-annual examination of candidates will be held during the annual meeting of the Board, at New York City, on December 12, 13, 14 and 15, 1948. The forms for this examination are closed, but forms are now open for the Spring examination which will be given during May, 1949. Exact dates and place will be announced later. All applications must be in the hands of the Secretary-Treasurer at least 90 days before the examination date.

The American Board of Radiology, B. R. Kirklin, M.D., Secretary-Treasurer, 102 2nd Ave., S.W., Rochester, Minn. The next scheduled examination will be held at Haddon Hall, Atlantic City, N. J., May 31–June 4, 1949.

The Royal College of Physicians and Surgeons of Canada, John E. Plunkett, M.D., Honorary Secretary, 150 Metcalfe St., Ottawa, Ont., Can. The

Annual Scientific Meeting of the College will be held at the Chateau Laurier Hotel, Ottawa, on November 26 and 27, 1948.

The Medical Society of the State of Pennsylvania held its Centennial Celebration Session at Philadelphia, October 3–7, 1948, with Dr. Edward L. Bortz, F.A.C.P., as Chairman of the Celebration Committee. Members of the American College of Physicians who presented papers included Dr. Kenneth E. Quickel, F.A.C.P., Harrisburg; Drs. Joseph T. Beardwood, Jr., Julius H. Comroe, Jr., Charles E. Brown, A. Reynolds Crane, Herbert T. Kelly, David W. Kramer, T. Grier Miller, Ralph Pemberton, Hobart Reimann, Stanley Reimann, T. G. Schnabel, W. D. Stroud, Joseph B. Vander Veer and Edward Weiss, Fellows, and Dr. Peter A. Herbut, Associate, all of Philadelphia; Dr. R. R. Snowden, F.A.C.P., and Drs. Robert C. Grauer and George E. Martin, Associates, Pittsburgh; Dr. Eli Eichelberger, Associate, York; Louis Krause, M.D., F.A.C.P., and Dr. Maurice C. Pincoffs, M.A.C.P., Baltimore, Md.; Elmer C. Bartels, M.D., F.A.C.P., Boston, Mass.; Hans H. Reese, M.D., F.A.C.P., Madison, Wis.

The Mississippi Valley Medical Society held its 13th Annual Meeting at Springfield, Ill., September 29–October 1, 1948. Dr. A. J. Carlson, M.A.C.P., Chicago, Dr. Arthur R. Colwell, F.A.C.P., Evanston, Ill., and Drs. L. T. Coggeshall, F.A.C.P., Paul S. Rhoads, F.A.C.P., Willard O. Thompson, F.A.C.P., and John B. Youmans, F.A.C.P., of Chicago, and Dr. R. O. Muether, F.A.C.P., St. Louis, were speakers.

During the recent International Medical Assembly of the Inter-State Postgraduate Medical Association of North America, which met at Cleveland, Ohio, November 9–12, 1948, the following Fellows of the College were speakers: Drs. Irvine H. Page and Robert D. Taylor, Cleveland, Treatment of Hypertensive Disease; Dr. Mavis P. Kelsey, Rochester, Minn., Treatment of Exophthalmic Goiter with Radio-iodine; Dr. Howard A. Rusk, New York, N. Y., Dynamic Therapeutics in Chronic Disease; Dr. Tom D. Spies, Birmingham, Ala., Recent Progress in Nutrition; Dr. E. Perry McCullagh, Cleveland, Testicular Dysfunction; Dr. Edward L. Bortz, Philadelphia, Management of Elderly Patients; Dr. Ray F. Farquharson, Toronto, Extreme Insufficiency of the Anterior Lobe of the Pituitary Gland; Dr. Walter Freeman, Washington, D. C., Use of Prefrontal Lobotomy in the Treatment of Pain; Dr. Cyrus C. Sturgis, Ann Arbor, Mich., Clinic Illustrating Newer Methods in the Treatment of Hematologic Disorders; Dr. Hans H. Reese, Madison, Wis., Multiple Sclerosis; Dr. Philip Levine, Raritan, N. J., Practical Application of Isoimmunization by the Rh Factor; Dr. John H. Talbott, Buffalo, N. Y., Gouty Arthritis; Dr. W. Philip Corr, Riverside, Calif., Diagnosis and Treatment of Cirrhosis of the Liver.

The Dallas Southern Clinical Society will hold its 1949 Annual Spring Clinical Conference on March 14–17. A. McGehee Harvey, M.D., F.A.C.P., Baltimore, Md., and Julian M. Ruffin, M.D., F.A.C.P., Durham, N. C., will be among the Honor Guest Speakers.

Samuel M. Jacobson, M.D., F.A.C.P., Cumberland, Md., addressed the Somerset County, Pa., Medical Society on September 21, 1948, on the subject "Congenital Heart Disease."

The University of California Medical School will offer during 1949 the following postgraduate courses of interest to internists: Cardiology, January 31–February 4; Endocrinology, including Diabetes, June 20–24; Diseases of the Chest, December 5–9. Inquiries and applications may be addressed to Stacy R. Mettier, M.D., F.A.C.P., Head of Postgraduate Instruction, The Medical Center, San Francisco 22, Calif.

DR. J. ROSCOE MILLER APPOINTED PRESIDENT OF NORTHWESTERN UNIVERSITY

The College has again been honored by the selection of one of its leading Fellows from Chicago for appointment to the presidency of an important university. In 1946 Dr. Raymond B. Allen, then Vice President of the University of Illinois, was elected President of the University of Washington. Recently, Dr. J. Roscoe Miller, Dean of Northwestern University Medical School since 1941, was appointed by the Board of Trustees of Northwestern University to succeed Dr. Franklyn Bliss Snyder as President of that institution on July 1, 1949.

Dr. Miller received the A.B. degree from the University of Utah in 1925, and the M.D. and M.S. degrees from Northwestern University in 1929 and 1931. Following internship at St. Luke's Hospital, Chicago, Dr. Miller became a member of the medical staffs of the Passavant and Wesley Memorial Hospitals. He was appointed Assistant Dean of the Northwestern University Medical School in 1933; Associate in Medicine, in 1937; Assistant Professor of Medicine, 1939; Dean and Associate Professor of Medicine, 1941. During the recent War, Dr. Miller served as Commander in the Medical Corps, U. S. Naval Reserve, as head of the Section on Internal Medicine in the Bureau of Medicine and Surgery, and he has since been appointed Consultant in Internal Medicine to the Surgeon General.

Dr. Miller is a diplomate of the American Board of Internal Medicine, in that specialty and in cardiovascular diseases. He was elected to Fellowship in the American College of Physicians in 1938.

Dr. Thomas Parran, F.A.C.P., who recently retired from the U. S. Public Health Service to become Dean of The School of Public Health of the University of Pittsburgh, has been honored by the award of the Distinguished Service Medal.

Pascal F. Lucchesi, M.D., F.A.C.P., Superintendent and Medical Director of the Philadelphia General Hospital, was recently selected for the award of the Dr. I. P. Strittmatter medal by the Philadelphia County Medical Society.

It was recently announced that Dr. C. Sidney Burwell, F.A.C.P., will relinquish on February 1, 1949, the Deanship of Harvard Medical School. He will, however, continue his activities as Research Professor of Clinical Medicine in the School, and at the Peter Bent Brigham Hospital.

Harold J. Harris, M.D., F.A.C.P., New York, N. Y., is a participant in The Second Inter-American Congress on Brucellosis at Mendoza, Argentina, November 17–22, and at Buenos Aires, November 22–26, with a paper on "Recent Advances in Diagnosis and Treatment of Chronic Brucellosis." Dr. Harris spoke before the Laboratory Section of the American Public Health Association, at the Annual Meeting in Boston on November 9, on "Chronic Brucellosis; The Unsatisfactory Status of Present Diagnostic Methods."

Dr. Karl Rothschild, F.A.C.P., New Brunswick, N. J., attended the International Congress on Mental Hygiene in London, England, August 16–21, 1948, as a delegate of the New Jersey Neuro-Psychiatric Association. He presented a short paper on the program.

Gift to the College Library of Publications by Members

Dr. William Gerry Morgan, M.A.C.P., Washington, D. C., has presented to the Library of the American College of Physicians a bound volume of all of his medical articles published since 1930, comprising a book of some formidable size. In autographing his gift to the Library, he added "presented to the Library of the American College of Physicians, not in the belief that anything in this volume has any special merit, but in the hope that it may stimulate other Fellows to do likewise." Dr. Morgan is one of the charter members of the American College of Physicians, served many years on its Board of Regents and on its Board of Governors and was at one time the Secretary General of the College.

Medical Society Executives Conference

The Medical Society Executives Conference is an Association of executive employees of national, state, regional and county medical societies, whose purposes are to enable medical society executives to improve the quality and efficiency of their services to their respective societies and to the medical profession generally; to provide a mechanism for the exchange of information and experience among medical society executives, for mutual improvement and for Fellowship.

The Conference was formally organized in 1947 and has held annual meetings since then. It numbers more than 120 members, including the vast majority of all eligible executive employees of recognized medical societies throughout the United States.

OBITUARIES

DR. EDMOND ELMORE BOHLENDER

Dr. Edmond Elmore Bohlender (Associate), Dayton, Ohio, died April 26, 1948, aged 80. He was a graduate of the Medical College of Ohio, 1894, was engaged in general medical practice, and for many years was a medical examiner for the Metropolitan Life Insurance Company. He became an Associate of the American College of Physicians by virtue of membership (1925) in the American Congress on Internal Medicine, an organization that was merged with the College in 1926, its members being automatically made Associates of the College at that time.

DR. WARREN COLEMAN

Dr. Warren Coleman, a native of Augusta, Ga., died there February 13, 1948, at the age of 79. The major part of his professional life was spent in New York City where he held appointment as Professor of Clinical Medicine and Applied Pharmacology in the Cornell University Medical College, 1909–18, and as Assistant Professor of Medicine, Professor of Clinical Medicine, and Professor Emeritus of Clinical Medicine, after 1918.

Dr. Coleman was a graduate of Transylvania College, from which he later received an Honorary A.M. degree. He obtained his M.D. degree from the New York University College of Medicine in 1891 and later took postgraduate studies at the Johns Hopkins University School of Medicine. During his long practice in New York, he achieved eminence through the innovations in diet in treatment of typhoid fever which he advocated. The reports of results which he had obtained from the use of full diet for typhoid patients led to their feeding rather than starving as had been previously customary. He served for many years on the staffs of the New York City Hospital, Lenox Hill Hospital, Bellevue Hospital, and shortly before his death he received a medal and citation, "for distinguished and exceptional public service," from the Commissioner of Hospitals of New York City. In 1938, Dr. Coleman returned to Augusta and accepted appointment as Professor of Clinical Medicine in the University of Georgia School of Medicine. He resigned this appointment in 1939 following a heart attack.

Dr. Coleman published many important and excellent papers during his long career, chiefly devoted to the subject of physical diagnosis. He was especially interested in the development of the sense of palpation and vibratory sense in physical examination. A master clinician, he delighted in teaching medical students the art of true physical diagnosis dependent upon the use of the five senses. A modest and unpretentious though eminent physician, Dr. Coleman took active interest in politics in Augusta and was instrumental in organizing the Citizen's Union and was a strong backer of the Independent Party. It is said that he served as the model for Colonel Effingham in the book, "Colonel Effingham's Raid."

CARTER SMITH, M.D., F.A.C.P.,
Governor for Georgia

DR. WILLARD D. KLINE

Willard Daniel Kline, M.D., was a favorite among his colleagues, and will be greatly missed. He was born in Allentown, Pa., on July 4, 1877, and died August 9, 1948.

Dr. Kline went to Muhlenberg College and obtained his B.A. degree in 1897. He took his medical training at Jefferson Medical College of Philadelphia, and received

his M.D. degree in 1901, subsequently serving his internship at The Lankenau Hospital, Philadelphia, where he received surgical training under the famed surgeon, John B. Deaver, M.D.

During the years 1905 to 1922, Dr. Kline was Physician to Muhlenberg College. From 1912 to 1920, he was Chief, State Tuberculosis Dispensary, and from 1920 to 1922, chest examiner, United States Veterans Bureau. Dr. Kline became Staff Physician to the Sacred Heart Hospital, Allentown, in 1916, and became Dean of its Medical Division in 1934.

Our friend is a past president of the Lehigh County Medical Society, and served as treasurer for a period of fifteen years.

Dr. Kline was a Fellow of the American Medical Association and became a Fellow of the American College of Physicians in December, 1939.

Dr. Kline's genial and kindly disposition will be missed by a host of friends, both in and out of the medical profession.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. SOLOMON SOLIS-COHEN

Dr. Solomon Solis-Cohen, the oldest living member of a family prominent in the life of Philadelphia since before the Revolution, died July 12, 1948, at the age of 90. He was an unusually gifted teacher, a sincere, honest, and devoted physician, and a zealous worker in many fields, in which he published actively.

Dr. Solis-Cohen received his Bachelor and Master of Arts degrees from Central High School, the M.D. and D.Sc. degrees from Jefferson Medical College of Philadelphia, D.H.L. from the Jewish Theological Seminary of America, and D.Sc. from the Philadelphia College of Pharmacy and Science. He began his career in the Out-Patient Department of the Jefferson Medical College Hospital in 1884 as Chief Clinical Assistant of that department. His first appointment to the faculty of the Jefferson Medical College of Philadelphia was in 1885 as Lecturer on Special Therapeutics. He became Assistant Professor of Medicine in 1902, Professor of Clinical Medicine, 1904, and served in the latter capacity until 1928 when he was appointed Emeritus Professor of Clinical Medicine. Dr. Solis-Cohen was also Consulting Physician to the Philadelphia General and Jewish Hospitals.

Dr. Solis-Cohen was a member of the Philadelphia County Medical Society, Medical Society of the State of Pennsylvania, the Pathological Society of Philadelphia, an Honorary Member of the Medical and Chirurgical Faculty of Maryland, the Lehigh Valley, Tri-State, and St. Louis Medical Societies. A Fellow of the American Medical Association, the Association of American Physicians, and the College of Physicians of Philadelphia, he was elected to Fellowship in the American College of Physicians in 1923.

Our Doctor was distinguished in many fields. He was among the first Americans, if not actually the first, to advocate the hydrotherapeutic management of typhoid fever. He was a Hebrew scholar and at times active in support of Zionist, and later non-Zionist, interests and in political affairs. He had a keen interest in music, and poetry was his hobby. John Greenleaf Whittier reprinted the famous, "I Know My Redeemer Liveth," in his anthology, "Songs of Three Centuries."

The passing of such a distinguished man will be a great loss to his friends and associates.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. WILLIAM PAYNE THOMPSON

Dr. William Payne Thompson, F.A.C.P., of Princeton, N.J., died suddenly August 10, 1948, at the New York Hospital, of a massive acute hemorrhage from a peptic ulcer.

Dr. Thompson was born April 16, 1897, in Tuxedo Park, N. Y. He prepared for and entered Yale, and in World War I was a member of the first Naval aviation unit organized at Yale. He subsequently transferred to Columbia University, N. Y., where he was graduated Bachelor of Science in 1921, and Doctor of Medicine in 1924. He interned at the Presbyterian Hospital, N. Y., 1924–26, and was Resident in Pathology and Assistant in Medicine at Johns Hopkins, 1926–28. Dr. Thompson served the Columbia University College of Physicians and Surgeons as Instructor in Medicine, Associate in Medicine and Assistant Professor of Medicine, successively. For a number of years he was Assistant Attending Physician at the Presbyterian Hospital.

In 1946 Dr. Thompson moved to Princeton, where he took an interest in New Jersey medicine and was made President of the Board of Managers, New Jersey State Hospital at Marlboro, member of the Staff of Mercer Hospital, Trenton, and Consultant in Medicine, Fitkin Memorial Hospital, Neptune. He was also Secretary of the Board of Trustees of Trudeau Sanitorium. He was a Fellow of the New York Academy of Medicine, former Treasurer of the American Society for Clinical Investigation, and a Fellow of the American College of Physicians since 1940.

Dr. Thompson was especially distinguished in the field of hematology and for his studies on disorders of the spleen. Among his significant medical contributions are his descriptions of tuberculous pericarditis in the aged; the experimental production of portal hypertension, calling attention to its relationship to splenic hypertrophy and the secondary effects on activity of the bone marrow; and his correlations between the blood picture in so-called aplastic anemia and bone marrow patterns. He was one of the founders of the Spleen Clinic at the Presbyterian Hospital, where, for the first time, internists, surgeons, hematologists and pathologists were joined in a group to study splenic diseases.

He was an enthusiastic and inspiring teacher, a keen and discerning internist, and a most efficient organizer of clinical material. For the past several years he was the victim of chronic ill health, yet he maintained to the point of his endurance a sincere devotion to his many fields of interest and gave much of this time and energy to philanthropic causes and worthy institutions. His numerous associates and friends deplore deeply his untimely passing.

FRANKLIN M. HANGER, M.D., F.A.C.P.

DR. HARLEY A. WILLIAMS

Dr. Harley A. Williams was born in Huron County, Ohio, on November 18, 1900, and died in Cleveland, March 5, 1948.

He received his A.B. degree from Oberlin College in 1923; his A.M. degree from the same school in 1925; and his M.D. in 1929 from Western Reserve University School of Medicine, where he stood at the head of his class and was honored by election to AOA. Dr. Williams interned and served as Assistant Resident in Medicine in the Lakeside Hospital, Cleveland, from 1929 to 1931. He joined the Faculty of the Western Reserve University School of Medicine in 1931 as Assistant Physician, advancing to Associate Physician and, ultimately, to the position of Physician-in-Charge of the Outpatient Department. In 1938 he was made Assistant Clinical Professor of Medicine. He was always fascinated by the possibilities presented in the teaching of physical diagnosis and was in charge of this course for a number of

years. Dr. Williams became a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians in 1937. He was active in the affairs of the Cleveland Academy of Medicine, serving on its Board of Trustees, and as Vice President in 1941.

As a house officer, Dr. Williams showed considerable curiosity, and, in addition to several brief clinical reports, showed that bovine was as effective as human gastric juice in producing remissions in pernicious anemia. But his love of people and of the immediate practice of medicine was too strong to permit him to yield to the intellectual satisfaction of an academic career. Because of his devotion to his patients, combined with exceptional diagnostic skill, his practice grew rapidly. He was much sought after as a consultant by younger men in his own city and in the surrounding counties. These calls he accepted eagerly and enthusiastically, both because of the challenge to his diagnostic skill and the opportunity it gave him to be of help to a colleague. He served as a good teacher in this role, as he did on the wards and in the Outpatient Department of the Lakeside Hospital. His chief interests aside from his profession and his family were the occasional hunting and fishing vacations which he enjoyed.

The sudden and untimely termination of the services to his community of this fine physician is deeply regretted by his numerous friends, students, and patients.

CHARLES A. DOAN, M.D., F.A.C.P.,
Governor for Ohio

DR. HENRY LEWIS COOPER

Dr. Henry Lewis Cooper was born in Philadelphia, Pa., on February 28, 1897. He was educated in Colorado, where he attended the University of Denver and obtained his medical degree from the University of Colorado School of Medicine in 1920. His internship was served at St. Luke's Hospital, Denver. All of Dr. Cooper's professional life took place in Colorado, and he became one of the outstanding internists and citizens of the region. He died suddenly on June 23, 1948.

Dr. Cooper's professional and civic activities were many and varied. At the time of his death, he was Assistant Professor of Medicine in the University of Colorado School of Medicine. He was active on the staffs of the Colorado General, Denver General, and Mercy Hospitals. He served for a great many years on the Medical Advisory Board of the National Jewish Hospital, and was Vice Chairman of the Board at the time of his death. He saw strenuous activity during World War II as a Major and Lieutenant Colonel in the Medical Corps, Army of the United States, attached to the Army Air Forces. Dr. Cooper became a Fellow of the American College of Physicians in 1940, and was an active member of the Denver County, Colorado State and American Medical Associations.

WARD DARLEY, M.D., F.A.C.P.,
Governor for Colorado

DR. PHILLIP HALLOCK

Dr. Phillip Hallock was born February 28, 1903, at Superior, Wis., and died in Los Angeles, June 29, 1948.

He attended the University of Minnesota, having been graduated from the medical school in 1929. He received his Master of Science degree in 1934. In 1936 he did postgraduate work in Amsterdam and London. From 1937 to 1940 Dr. Hallock was an Instructor in Medicine in the University of Minnesota Medical School, and was made Assistant Professor in 1940. During World War II, he served in the Medical Corps, Army of the United States, from February, 1942, to January, 1946.

and was discharged with rank of Lieutenant Colonel. Dr. Hallock subsequently established residence and practice in Los Angeles.

Dr. Hallock was a member of the Los Angeles County Medical Association, the Hennepin County and Minnesota State Medical Societies, Minnesota Society of Internal Medicine, Central Society of Clinical Research, American Heart Association, American Association for the Advancement of Science, American Society for Clinical Investigation; he was a Fellow of the American Medical Association, and, in 1940, became a Fellow of the American College of Physicians.

Dr. Hallock was respected and admired by his fellow practitioners. A great deal of his time was devoted to consultations at local Veterans Hospitals in this vicinity.

LELAND HAWKINS, M.D., F.A.C.P.,
Governor for Southern California

DR. LAWTON M. HARTMAN, JR.

Dr. Lawton Mervale Hartman died October 6 at his home in York, Pa., after a long illness, following a cerebral hemorrhage. He was 69 years old.

Dr. Hartman attended the York Collegiate Institute and obtained the M.D. degree from the University of Pennsylvania School of Medicine in 1902. After an internship at Howard Hospital, Philadelphia, he returned to York and served three years at the York Hospital as interne. In 1906 he went to Europe, spending a year and a half in travel and medical study in Vienna. In 1907 he was appointed to the York Hospital medical staff and for 16 years was chief of its cardiovascular service. He also served for 18 years on the visiting staff of the Children's Home. During World War I he volunteered for service and was commissioned a captain in the Medical Reserve Corps. Since then he continued the practice of medicine in York.

Dr. Hartman was a life Fellow of the American College of Physicians, a Fellow of the American Medical Association, a member of the Medical Society of the State of Pennsylvania, the American Heart Association, and the York County Medical Society, whose president he was in 1911.

Dr. Hartman was an intense and profound student of medicine, especially interested in diseases of the cardiovascular system. As a diagnostician and consultant, he enjoyed a well earned reputation in York County and vicinity. Gifted with a friendly, sympathetic personality, he was able to achieve much in his career that scientific medicine alone would scarcely have accomplished. Modest and self-sacrificing, he was entirely devoted to family, friends, colleagues and patients, and he will long be remembered by all of them as a most thoughtful, studious physician whose decisions were made only after most thorough investigation and careful deliberation.

JULIUS H. COMROE, SR., M.D., F.A.C.P.

DR. WILLIAM WILLIAMSON JARRELL

William Williamson Jarrell, M.D., F.A.C.P., was born in Cartersville, Ga., September 22, 1876. He died in Thomasville, Ga., June 21, 1948, from prostatic hypertrophy, complicated by chronic nephritis and uremia. He received his A.B. degree from Emory College in 1897 and was graduated from the Vanderbilt University School of Medicine in 1901. Dr. Jarrell took postgraduate work at the New York Polyclinic Medical School and Hospital and the Harvard Medical School.

Dr. Jarrell served in World War I as a major in the Medical Reserve Corps. He was a member of the senior medical staff of the John D. Archbold Memorial Hospital and was especially interested in cardiovascular-renal disease.

Dr. Jarrell was a member of the Thomas County Medical Society, the Second District Medical Society, the Medical Association of Georgia, and the Southern Medical Association, a Fellow of the American Medical Association and, since 1929, a

Fellow of the American College of Physicians. In his death the community lost a capable physician on whom countless people depended.

CARTER SMITH, M.D., F.A.C.P.,
Governor for Georgia

DR. OZA J. LaBARGE

Dr. Oza Joseph LaBarge, Chief of Medical Service of the Veterans Administration Hospital, Alexandria, La., died July 28, 1948. Dr. LaBarge had been a Fellow of the American College of Physicians since 1932.

Born March 30, 1898, at Standish, Mich., Dr. LaBarge received his premedical and medical training at the University of Michigan, where he obtained the B.S. degree in 1921 and the M.D. in 1923. He subsequently engaged in the practice of medicine in Salt Lake City, where he held appointments as Instructor in Medicine in the University of Utah School of Medicine, as Junior in Medicine at the Latter Day Saints Hospital and as Senior Internist for the Union Pacific Railroad Company. Dr. LaBarge entered the Army in 1940 with rank of Lieutenant Colonel, and was assigned to the Station Hospital, Camp Livingston, La., where he served as Chief of Medical Service until July 12, 1944. He was then assigned to the 179th General Hospital as Chief of Medical Service, and was later appointed its Commanding Officer, with rank of Colonel. This Hospital was assigned to the European Theatre of Operations with station in the United Kingdom. Dr. LaBarge was separated from the service in May, 1946, and soon thereafter accepted his first assignment in the Veterans Administration as Chief Medical Officer of the Regional Office in Lubbock, Tex.

Dr. LaBarge was a diplomate of the American Board of Internal Medicine, a member of the Salt Lake County, Utah State and Pacific Northwest Medical Associations, of the Pacific Association of Railway Surgeons and the American Heart Association, and a Fellow of the American Medical Association.

COLONEL CHARLES W. SALE, (M.C.), U.S.A., Ret'd

Colonel Charles Wallace Sale, Medical Corps, U. S. Army, Retired, died July 10, 1948, at Fredericksburg, Va., as the result of a cerebral hemorrhage.

He was born March 25, 1885, in Sealston, Va.; received his M.D. degree in 1907 from the University College of Medicine (Richmond); interned at the Retreat for the Sick, in Richmond, and was commissioned a First Lieutenant, Medical Corps, Regular Army, September 10, 1917, after serving a little more than three years in the Medical Reserve Corps.

During the First World War he served with the American Expeditionary Forces in France. After a short assignment in a General Hospital at Hampton, Va., he completed the course at the Army Medical School, Army Medical Center, Washington, D. C., and the indoctrination course at Medical Field Service School, Carlisle Barracks, Pa., and then was transferred to Camp Holabird, Md. In October, 1922, he became a Professor of Military Science and Tactics at the Medical College of Virginia, Richmond, and during his two years there did an excellent job. At three different times in his career he was stationed in the Philippines. Other short-term assignments include Army and Navy General Hospital, Hot Springs, Ark.; Fort Sill, Okla.; Fort Humphreys, Va.; and Fort Banks, N. Y. From March, 1941, until December, 1945, he performed duties of Chief of the Medical and Professional Services at Stark General Hospital, Charleston, S. C., and was very highly respected at that station. He was retired from service on May 31, 1946, with rank of Colonel.

CLIFFORD G. BLITCH, F.A.C.P.,
Colonel, (M.C.), U. S. Army